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OCCURRENCE OF PERITONITIS DURING ACTH ADMINISTRATION*

J. C. Beck, M.D., J. S. L. Browne, M.D., L. G. Johnson, M.D., B. J. Kennedy, M.D. and D. W. MacKenzie, M.D.

Montreal, Que.

IN investigations of clinical and metabolic effects of adrenocorticotropic hormone (ACTH) and cortisone acetate, it is increasingly apparent that many of the common criteria employed in the diagnosis and evaluation of diseases are no longer valid. In various conditions generally associated with fever, it is now established that with a sufficient dose of ACTH the temperature and pulse rate return to normal levels usually within 12 to 36 hours of the initial administration of the hormone.[1 to 6]

ACTH is usually administered every six hours, since the effects of this hormone are transient.[7, 8, 9] It has been demonstrated that upon omission of a single injection of ACTH, reduction of the dose, or upon cessation of the hormone while the disease process is still active, the temperature and pulse rate again promptly increase.[1 to 8] Similarly, the common hæmatological criteria used in diagnosis are altered. The sedimentation rate returns to normal when an adequate amount of ACTH is given in those cases in which it is elevated. Following an initial decrease of the total leucocyte count in the first 1 or 2 hours after commencing ACTH, the white blood count then increases in normals and in many disease states. This increase is the result of an absolute increase in the polymorphonuclear cells with an increase of stab forms. The differential blood count is further altered by the lymphopenia and eosinopenia which occur during ACTH administration.[1, 7, 9 to 12]

Two cases of acute peritonitis occurring as a complication during ACTH† administration, one a case of Hodgkin's disease and the other of periarteritis nodosa, presented in this report have shown sufficient alteration in the usual signs and symptoms to confuse the accurate diagnosis of this acute abdominal emergency. These are presented as a further demonstration of the altered response of the human organism while receiving ACTH. It is suggested that these differences in response be considered when changes in or development of new signs or symptoms occur in patients receiving ACTH or cortisone. Complete clinical and metabolic data will be presented at a later date.

CASE 1*

In June, 1948, this 48-year old farmer developed low back pain radiating into the legs, intermittent fever and increased fatiguability. The only previous illness was a diverticulitis confirmed by an exploratory laparotomy in May, 1948. Progressive weakness of the right leg during a two week period necessitated hospitalization in January, 1949. Examination revealed a spiking fever, axillary and inguinal lymphadenopathy, hepato- and splenomegaly, anæmia, eosinophilia, and extradural infiltration of the lumbar-sacral area on x-ray. A lymph node biopsy was characteristic of Hodgkin's lymphoma. Improvement followed nitrogen mustard therapy and irradiation of the lumbar spine. Six months later reactivation of the disease was again successfully treated with nitrogen mustard and irradiation of a mass over the sternum.

The patient was readmitted in December, 1949, because of weakness, pallor, and generalized œdema of one month's duration. Physical examination revealed evidence of weight loss, enlarged axillary and inguinal lymph nodes, a palpable liver four fingersbreadth below the costal margin, moderate œdema of the ankles and legs, and mild œdema of the hands. Urinalysis demonstrated 2 to 4 plus albuminuria and occasional white blood cells, red blood cells and granular casts. The specific gravity was fixed at 1.010. The hæmoglobin was 8.0 gm. and the white blood count 46,000 with 13,325 eosinophils. The non-protein nitrogen was 102 mgm. %; total protein, 5.47 gm. %; albumin, 2.08 gm. %; globulin, 3.39 gm. %; serum calcium, 5.85 mgm. % and serum phosphorus, 8.98 mgm. %. There was 96.8% absorption in one hour of the Congo red dye. A lymph node biopsy was again characteristic of Hodgkin's lymphoma with marked eosinophilic infiltration. Investigation of the effect of ACTH in this patient with Hodgkin's disease and associated amyloidosis was begun.

The initial dose of ACTH was 100 mgm. per day in four divided doses. This produced a decrease of the eosinophils to 4,000. An increase of the eosinophils to 8,000 on the eighth day suggested an apparent escape from the effect of ACTH, and hence the dose was increased to 200 mgm. daily. A second reduction of the eosinophils to 8 per c.mm. followed. The dose of ACTH was reduced to 150 mgm. daily on the 14th day and continued for a further eight days. The patient received ACTH for 21 days.

* From the McGill University Clinic and the Department of Surgery, Royal Victoria Hospital, Montreal, Que.

† The ACTH was generously supplied by Dr. John R. Mote of the Armour Laboratories, Chicago.

* This patient was placed on study through the courtesy of Dr. Joseph Kaufmann.

During the administration of ACTH this patient's condition gradually deteriorated. There was persistent nausea, occasional vomiting, weight loss of 22 pounds, and severe retrosternal burning only partially relieved by anti-acids.

There was a decrease in size and increased firmness of the axillary and inguinal lymph nodes. Serial bone marrow aspirations showed a marked reduction of the eosinophilic infiltration. A similar change was demonstrated in a lymph node biopsy on the 9th day.

The non-protein nitrogen slowly increased to 189 mgm. %, the Congo red dye test remained unaltered, the hæmoglobin was below 8.0 gm. and the white blood count which had been 47,000, had decreased to 20,000 and remained at that level.

On the 18th day of ACTH administration the patient developed an upper respiratory infection with a mild cough. The temperature, pulse and respirations were normal. The white blood count had further decreased to 10,800. Chest examination revealed a few rhonchi over both bases posteriorly with slight diminution of breath sounds over the right base.

At 2.00 a.m. of the 20th day, the patient awakened with severe, generalized abdominal pain, most marked in the peri-umbilical area. At 8.00 a.m. an involuntary defæcation occurred. The benzidine test for occult blood in the stool was negative. Examination revealed the patient to be quite apprehensive and complaining of generalized abdominal pain. The temperature was normal, the pulse rate varied between 80 and 100 per minute, and the respirations were increased in rate and depth suggestive of an early acidosis. Physical findings in the chest had not altered from the previous examination. There was generalized tenderness and slight tenseness of the abdominal wall, but no true rigidity and the abdominal wall moved freely on respiration. There was no rebound tenderness, no palpable organs or masses, no free fluid and no obliteration of liver dullness. However, no borborygmi could be heard on auscultation. During this examination pain was increased by shifting position or coughing. While moving the patient there was a sudden pain in the left shoulder, followed later in the day by a similar pain in the right shoulder. Generalized abdominal and bilateral shoulder pain continued to be prominent features. There was nausea with intermittent vomiting during the day. X-ray film of the abdomen and chest revealed no free gas present in the peritoneal cavity, a few dilated loops of small bowel, and a questionable pneumonia of the right lower and right middle lobe. The white blood count was 14,000 and the eosinophil count 8 per c.mm. The CO_2 combining power was 21 volumes %.

In view of the previous history of diverticulitis and the epigastric and retrosternal distress present during the latter part of the present illness, tentative diagnoses of diverticulitis, diaphragmatic pleurisy, or perforated peptic ulcer were considered. Surgical opinion concurred in this but did not feel that laparotomy was indicated in view of the patient's general condition. Treatment was supportive with intravenous 6 molar lactate and glucose-saline solutions and at 8.00 a.m. the last dose of ACTH was given. That afternoon at 2.00 p.m. the patient's condition became worse, the temperature was 101.4° F., (rectal), pulse 100 and the blood pressure was unaltered. A friction rub was audible over the right base with scattered rhonchi, but no râles. The left chest was clear. Penicillin, oxygen and i.v. fluids were administered, but the patient died that afternoon.

Post mortem examination revealed generalized Hodgkin's disease with amyloid deposits in the liver, kidney and spleen. There was an acute bronchopneumonia of the right upper and lower lobes with an acute fibrinous pleurisy over the inferior surface of the right lower lobe. There was an acute generalized peritonitis with 2,800 c.c. of fibrino-purulent fluid, but no fresh adhesions. Culture of this fluid revealed a heavy growth of pneumococci as did a post-mortem culture of the blood in the heart. Other post-mortem findings were marked hypertrophy of the adrenal glands, the right weighing 17 grams and the left 15 grams (normal 8 grams), and failure of healing of biopsy incisions, the first in the inguinal region having been made the day prior to and the second in the right axilla on the 9th day of ACTH administration.

CASE 2

This 34-year old Jewish female developed nasal obstruction in November, 1949, with an associated productive cough. A right radical antrum operation and submucous resection for sinusitis were performed at another hospital. At that time wheezing and expiratory distress occurred suggestive of asthma. Because of failure of the above complaints to improve following the operation, penicillin, streptomycin and autogenous vaccines were employed without success.

Three months later the patient developed fatigue, anorexia, vague pains in the thighs, calfs, ankles and hands, and coldness and numbness of all extremities.

During February, 1950, there was rapid development of paræsthesias and anæsthesia of the hands and feet. Physical examination revealed bilateral wrist and foot drop and painless decubitus ulcers on both elbows. Vibration sense was absent over the extremities. The white blood count varied between 19,000 and 30,000 with 20 to 44% eosinophils. The sedimentation rate was markedly elevated and the urinalysis was normal. During hospitalization the patient had several episodes of diarrhœa. A benzidine test for occult blood was 4 plus. A gastrocnemius muscle biopsy revealed periarteritis nodosa. An investigation of the effect of ACTH on this disease was commenced.

ACTH, 100 mgm. daily in four divided doses intramuscularly, was begun. The white blood count decreased to 13,900, and the eosinophil count, initially 5,172, fell to 14 per c.mm. by the 4th day. The patient had an increased feeling of well being and an increase in appetite. Paræsthesias in the extremities became more severe and pain appeared in decubitus ulcers of both elbows on the third day of ACTH administration.

At 3.30 p.m. on the seventh day the patient developed severe crampy pain in the left side of the abdomen. This was accompanied by a loose bowel movement which contained no gross blood. The pain was crampy and accompanied by passage of large amounts of flatus. Examination revealed a normal temperature, a pulse rate of 80 to 90 per minute and a normal blood pressure. There was slight resistance in the left upper quadrant with moderate tenderness and rebound tenderness. No distension was present. Peristaltic rushes could be felt in the abdomen and borborygmi were audible. No costo-vertebral tenderness was evoked.

No flatus was passed after 6.00 p.m. and the abdominal pain became more severe and generalized. Nine hours after the onset of the pain the physical findings were essentially the same except the tenderness was generalized and no rigidity was demonstrated.

A review of the patient's past history revealed the occurrence of bouts of post-prandial epigastric fullness and crampy pain. In 1947, after x-ray study of the gastro-intestinal tract with negative findings, a diagnosis of "nervous" stomach was made and the patient was urged to seek psychiatric aid because of marked emotional instability.

The following morning the pain was extremely intense and crampy. At this time there was marked generalized abdominal and costo-vertebral tenderness, minimal

resistance, and absent peristaltic sounds. The temperature, pulse and respirations were unchanged. The patient volunteered that she felt that there was fluid in the abdominal cavity, but none could be demonstrated. The white blood count was 36,400, a rise of 23,000 from the fourth day. X-rays of the abdomen revealed no free gas or distended bowel loops. There was no nausea or vomiting at any time. During the day the intense abdominal pain continued and the patient's condition was worse. Twenty-four hours after the onset of the pain, the temperature was 99.8° F. and the pulse 100.

On examination by the surgeon (D.W.M.) at this time the patient appeared acutely ill. She was pale, listless and obviously in considerable pain which she referred to her entire abdomen.

The abdomen was moderately and symmetrically distended. It presented no scar or hernia. Palpation revealed little if any increase in muscular resistance. Tenderness was diffuse. In fact the patient was as tender deep in the flank muscles as she was anteriorly. There were no palpable masses. Liver dullness was diminished. Though it was felt that free fluid was present, it was not conclusively demonstrated at this examination. Rectal examination was negative. The outstanding feature at this point was that repeated attempts failed to elicit the slightest sound of peristalsis. Medical and surgical opinions concurred in the advisability of an exploratory laparotomy with a tentative diagnosis of mesenteric thrombosis secondary to the periarteritis nodosa.

Upon exploration three hours later a generalized peritonitis was apparent. There was fluid, creamy yellow pus in the pelvis, both lumbar gutters, behind the liver and beneath the left diaphragm. A four mm. diameter perforation was observed on the anterior surface of the first portion of the duodenum. Because of its pinkish coloration and soft resilient consistency, this ulcer appeared to be acute. There were no surrounding flecks of fibrin and no attempt had been made by the omentum or other neighbouring structures to wall off the perforation.

The ulcer was closed with three interrupted fine chromic catgut sutures, which did not tear through the tissue and upon which was sewn a small pad of omentum. The peritoneal cavity was aspirated and wiped as clean as possible. Four grams of powdered streptomycin were instilled. The incision was closed in layers with stainless steel wire. It was not drained. Intramuscular penicillin and streptomycin therapy was begun prior to the laparotomy. Bacteriological examination of the peritoneal exudate revealed a light growth of *Staph. pyogenes* and *Strep. bovis.*

Up to the time of writing, her sixteenth postoperative day, the patient's course has been entirely uncomplicated. The highest temperature recorded was 99.4° F., the pulse rate fell below 80 within 48 hours of the operation. There has been no abdominal distension and no pain other than might be accounted for by the incision, which is healing cleanly with sutures still in place. ACTH administration has been continued 80 mgm./day for 3 days, then 60 mgm./day for one day and at the present time the patient is receiving 40 mgm./day. This gradual reduction in dosage has been carried out in an attempt to promote better conditions for wound healing.

From the surgical point of view this case presented several interesting deviations from the average. It is noteworthy that in the presence of a generalized peritonitis the temperature and pulse rate were practically normal and that muscular resistance was not increased. Objectively the two essential criteria for operation were absent peristalsis and diminished liver dullness. At operation it was surprising to find that no attempt had been made to wall off the perforation. The absence of fibrin in the peritoneal exudate was quite striking.

DISCUSSION

These two patients presented certain deviations from the usual picture of acute peritonitis. In the first patient there was no fever, a normal pulse rate, no leucocytosis and no rigidity. The features of the underlying condition present were pain and the absence of peristaltic sounds. In the second patient there was no fever initially, a normal pulse rate and an absence of muscular rigidity. The signs and symptoms present were pain, absent peristaltic sounds, diminution in liver dullness and a probable rise in the white blood cell count.

It is true that absence of rigidity may occur late on in peritonitis but both these individuals were in hospital at the time of onset of their symptoms and thus both were promptly observed. It is also true that in elderly and in markedly debilitated patients fever, leucocytosis and rigidity may be very much less than is uusually observed. Neither of these patients fell into this category. The patient with Hodgkin's disease, though severely ill was able to sit up on the day prior to the acute episode. The patient with periarteritis nodosa was active and about the ward prior to the onset of her symptoms.

It is realized that two cases are too few upon which to base any conclusions, but it was felt that attention should be drawn to the probable obscuring of certain signs and symptoms of acute abdominal emergencies occurring while patients are receiving ACTH.

The problem as to whether the development of pneumococcal peritonitis in one case and perforation of an acute ulcer in the other were related to ACTH administration is not certain. It is possible that the peritonitis may have been occasioned by bacterial spread from the pulmonary lesion since Finland[2] has found a bacteræmia occurring during ACTH administration to a case of lobar pneumonia in the absence of the usual signs and symptoms of septicæmia.

The ulcer, which was apparently acute, may have been associated with a thrombosis as a feature of the periarteritis nodosa or for some other reason. It is true that the absence of cellular reaction which might be expected under ACTH administration would not have encouraged healing and it is possible that the absence of fibrin formation and adhesions found at laparotomy were consequent upon the administration of ACTH.

SUMMARY

Two cases of acute peritonitis, one associated with perforated duodenal ulcer, are presented.

These cases showed absence of fever and abdominal rigidity but pain and absent peristaltic sounds were present.

Both were receiving ACTH at the time of onset of symptoms. Some of the important signs and symptoms of acute perforation and peritonitis appeared to be obscured during the administration of ACTH thus making the diagnosis difficult.

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Œsophagoscopy is a valuable diagnostic procedure in hæmorrhage from the upper gastro-intestinal tract. Gastric surgery may be obviated and bleeding from œsophageal varices may be arrested by compression with oxycel-gauze tampons introduced through the œsophagoscope. Œsophagoscopy may be carried out as a bedside procedure in seriously ill patients, as was done in 9 of the 14 patients forming the basis of this report.—Carter, M. G. and Zamcheck, N.: *New England J. Med.*, **242**: 280, 1950.

THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) ON BERYLLIUM GRANULOMATOSIS*

A PRELIMINARY REPORT

B. J. Kennedy, M.D., J. A. P. Pare, M.D., K. K. Pump, M.D. and R. L. Stanford, M.D.

Montreal, Que.

STUDIES of the response of rheumatoid arthritis to cortisone recorded a lowering of the concentrations of serum globulin and return to normal of albumin-globulin ratios.[1] Other observations have demonstrated alterations in cellular and fibrous tissue reactions when this adrenal hormone or ACTH were employed.[2, 3] In conjunction with investigations relative to the effect of adrenocorticotropic hormone (ACTH) in disease, it was postulated that since beryllium granulomatosis was characterized by excessive fibrous tissue and cellular reaction in the interalveolar septæ and occasionally by hyperglobulinæmia, an alteration of the disease process might occur with adrenocorticotropic hormone administration.

Beryllium granulomatosis (delayed chemical pneumonitis) is a progressive pulmonary disease occurring in employees of industries using beryllium. Common symptoms are fatigue, exertional dyspnœa, cough and weight loss. X-rays demonstrate diffuse pulmonary changes.[4, 5] Microscopically the lesions consist of multiple, scattered granulomas, increased fibrosis in the interalveolar septæ and in the granulomas, dense collagen deposits and cellular infiltration.[6] It appeared that if these lesions resolved, the impairment of pulmonary circulation and air exchange would be diminished, and more normal respiratory function might occur. Furthermore, the onset of the disease following pregnancy suggested a possible hormonal relationship.[5, 7] Hence, a patient with beryllium granulomatosis was studied.†

The purpose of this report is to record briefly observations made during the investigation. Complete metabolic data and respiratory studies will be presented at a later date.

* From the McGill University Clinic, Royal Victoria Hospital, Montreal.

† We are indebted to Dr. Stanley Wilson for aid in arranging for investigation of this patient, and to the Sylvania Electric Products, Inc., for financial aid.

CASE REPORT

This 27 year old man was employed in a fluorescent lamp manufacturing plant from September 6, 1940, to April 3, 1943, where exposure to beryllium dust occurred. In July, 1947, cough, dyspnœa on exertion, anorexia, weight loss of 10 pounds and weakness began. A chest x-ray revealed a diffuse granulomatous process in both lungs with hilar node enlargement. During the ensuing two years the disease gradually progressed, as evidenced by marked dyspnœa even on mild exertion, and an increase in the extent of the pulmonary lesions.

The patient was admitted to the McGill University Clinic of the Royal Victoria Hospital on January 21, 1950, for study. Chief complaints continued to be fatigue, weakness, dyspnœa, and mild cough. Examination revealed an asthenic man. The respiratory rate was increased at rest, being usually about 28 per minute. There was intercostal retraction low in the chest on inspiration. Many fine, moist, crackling râles were present throughout the entire chest. The pulmonic second sound was accentuated, the heart size normal, and numerous extrasystoles were present. Moderate clubbing of the fingers was noted.

Laboratory studies revealed a polycythæmia: hæmoglobin 18.4 gm.; 6.0 million red blood cells; 5,700 white blood cells and 50.5% hæmatocrit. The total protein was 9.15 gm. with the albumin, 5.5 gm. and globulin, 3.65 gm.

Respiratory studies demonstrated considerable reduction of maximum breathing capacity and vital capacity. Hyperventilation was present at rest and was markedly increased with only moderate exercise. Oxygen absorption was impaired as judged by the relation between total ventilation and oxygen consumption during exercise. Arterial oxygen saturation was low. Despite an increase in residual air, suggestive of the development of emphysema, the total lung capacity was somewhat diminished. The findings were in accord with those previously reported to occur in patients with beryllium granulomatosis.[8, 9]

X-rays of the chest revealed prominent pulmonary markings and a diffuse infiltration with micronodular densities. The hilar nodes were enlarged (Fig. 1).

The patient was placed on a constant diet and balance studies were carried out. Following a two week control period, adrenocorticotropic hormone (ACTH), 25 mgm. four times a day intramuscularly, was commenced February 7, 1950, and continued 28 days.*

RESULTS

During the four weeks of ACTH administration a striking subjective improvement occurred. There was an increased feeling of well being. Towards the end of the period of ACTH, increased aggressiveness and emotional instability necessitated discontinuance of the hormone.

During the first week of ACTH injections the pulmonary râles gradually disappeared, and the lungs remained clear on auscultation thereafter. Concomitant with this change, the patient noted a decrease in dyspnœa on exertion. The third week, climbing four flights of stairs produced no distress, though before ACTH was begun a few steps produced severe dyspnœa. The resting respiratory rate decreased, and the pulmonic second sound became less accentuated. There appeared to be no clinical impairment of respiratory function at the time ACTH was discontinued.

Lung volume studies and maximum breathing capacity demonstrated progressive improvement throughout the period of investigation. The vital capacity was increased by more than one litre. The residual air decreased to within normal range. Maximum breathing capacity increased from 55 to 115% of the predicted normal value. A decrease in minute ventilation and an increase in oxygen absorption at rest and with exercise confirmed the clinical impression of a return toward normal in pulmonary efficiency.

X-rays demonstrated a gradual decrease in pulmonary markings, an apparent decrease in size and density of

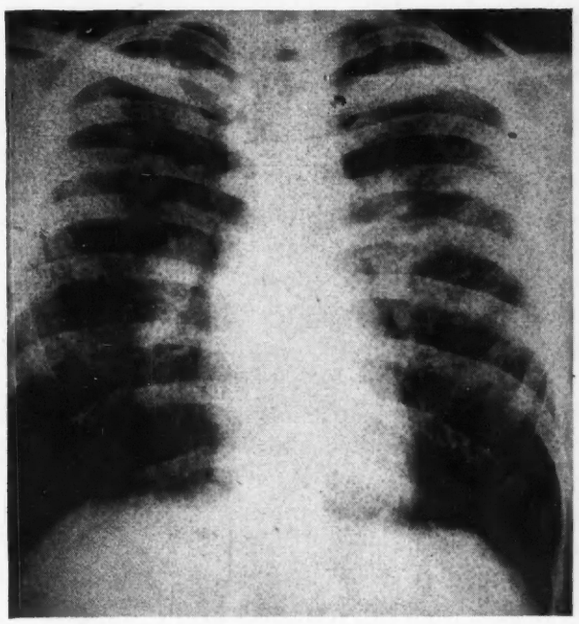

Fig. 1

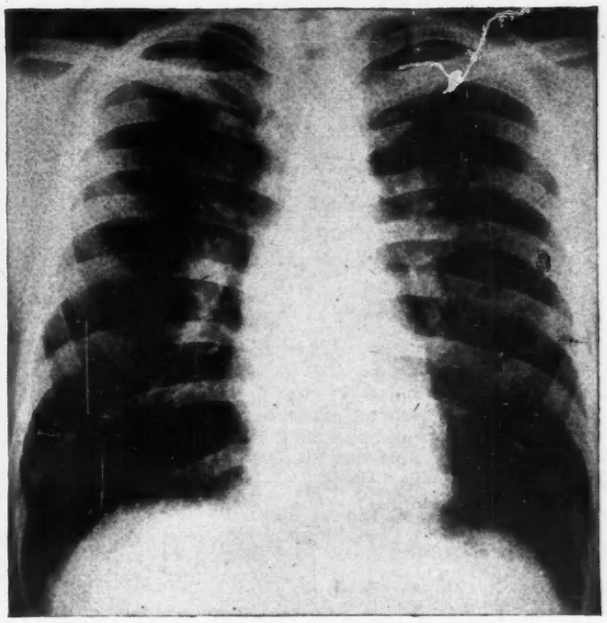

Fig. 2

Fig. 1.—Appearance of the lungs prior to ACTH administration. **Fig. 2.**—Decrease in size of hilar nodes and decrease in density of pulmonary nodules after the third week of ACTH administration.

* The ACTH was generously supplied by Dr. John R. Mote of the Armour Laboratories, Chicago.

nodules, decrease in the size of hilar nodes, and clearing of the lungs (Fig. 2). The nodular densities, however, had not entirely disappeared. Ten days after cessation of ACTH, a few patchy densities had reappeared, but the improvement of the clinical status and respiratory function had not altered.

CONCLUSION

Adrenocorticotropic hormone (ACTH) has been administered to a patient with beryllium granulomatosis. A striking improvement occurred as evidenced by the clinical response and improvement in x-rays and respiratory function studies.

Remissions in beryllium granulomatosis have not occurred with the use of other agents, and regressions such as demonstrated in this patient are regarded as unlikely to occur spontaneously.[10 to 12] The response of this patient to ACTH, demonstrates a temporary improvement, and suggests that this disease is reversible. It is obvious that follow up studies are necessary to determine the duration of improvement.

No attempt has been made to explain the mode or site of action of the adrenocorticotropic hormone. Complete metabolic data and progress of this patient will be presented in a future report.

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Studies on 32 patients showed that enteric-coated aspirin had an analgesic effect equal to that of plain aspirin; its onset of action was only slightly delayed and it was better tolerated than the ordinary form of the drug. Enteric-coated aspirin is especially useful where there is need for high dosage of salicylates or in peptic ulcer.—Talkov, R. H., Ropes, M. W. and Bauer, W.: *New England J. Med.*, **242**: 19, 1950.

ACTH IN ATOPIC DERMATITIS (INFANTILE ECZEMA) AND ASTHMA

B. Kanee, M.D., J. H. B. Grant, M.D., J. Mallek, M.D., M.Sc. and J. Eden, M.B., B.S.*

Vancouver, B.C.

THE dramatic results observed by Hench and co-workers[1] in the use of cortisone and ACTH in rheumatoid arthritis, stimulated our interest in the potentialities of these hormones in allergic diseases. For more than twenty years, Hench noted the fact that rheumatoid arthritis improved during jaundice and pregnancy. Similar observations were recorded by Rose[2] regarding the amelioration of asthma during pregnancy. Over the course of years, dermatologists found that atopic eczemas frequently underwent complete remission following non-specific factors such as febrile illnesses. This observation led to the use of non-specific fever therapy (typhoid vaccine) in atopic eczema. The results obtained were dramatic at times, with complete involution of the eczema during the course of therapy but relapse nearly always occurred shortly thereafter.

As these diseases (arthritis, asthma and atopic eczema) appeared to follow a somewhat similar pattern in their behaviour and in their response to non-specific stress, we felt that there was every possibility that ACTH and cortisone would prove as beneficial in atopic eczema as they have appeared to be in the control of rheumatoid arthritis[1] and asthma.[2, 3]

This report describes the very striking and beneficial results seen during the administration of pituitary adrenocorticotropic hormone (ACTH) to an infant suffering from generalized eczema and asthma since the age of 3 and 12 weeks respectively, and who was able to be discharged home after a 7-month period of hospitalization. Laboratory studies and subsequent follow-up observations are also reported.

The age of this patient limited laboratory studies to those which could be performed readily on capillary blood, and similarly no absolute estimations of urinary constituents were attempted owing to the practical difficulty of obtaining complete urine volumes in a baby being nursed in a general pædiatric ward.

A standard dietary regimen was instituted and circulating eosinophils were counted at 8.30 a.m. and 2.00 p.m. daily, using the method

* Chemical Pathologist, Vancouver General Hospital.

recommended by Thorn[4] (Fig. 1). Sugar and urea nitrogen concentrations in capillary blood were estimated daily at 8.30 a.m. by the micro Folin Wu and urease Nesslerization methods respectively. Non-catheter specimens or urine were obtained before each 9.00 a.m. injection of ACTH and usually a second specimen was collected before 1.00 p.m. These were examined for protein (salicylsulphonic acid), reducing substances (Benedict's qualitative), ketone bodies (Rothera's test), creatinine (Jaffe reaction), uric acid (modified Folin) and urea (alkaline hypobromite), the methods used being

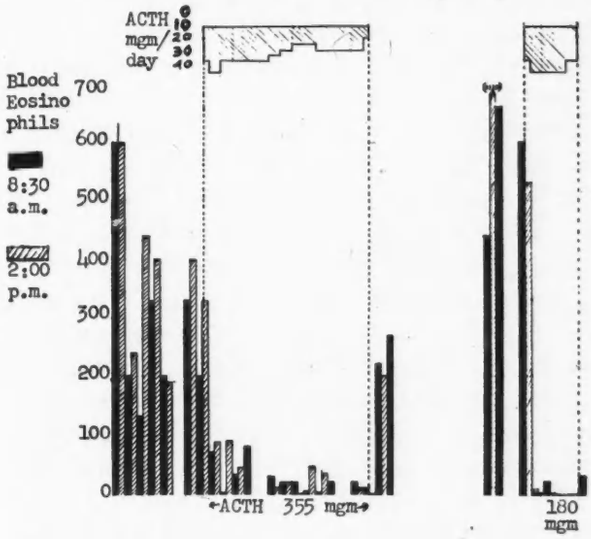


Fig. 1.—Graphic representation of the eosinophil counts and ACTH therapy.

shown in parenthesis. On one occasion, when the clinical condition was critical and perplexing, the packed cell volume of venous blood (Wintrobe), plasma chlorides (dichloro [R] fluorescein), serum sodium (modified McCance & Shipp) and serum potassium (modified Jacobs Hoffman) were estimated by the methods noted. On this day (January 24) pharyngeal swabs were obtained and examined by Dr. W. H. Cockcroft.*

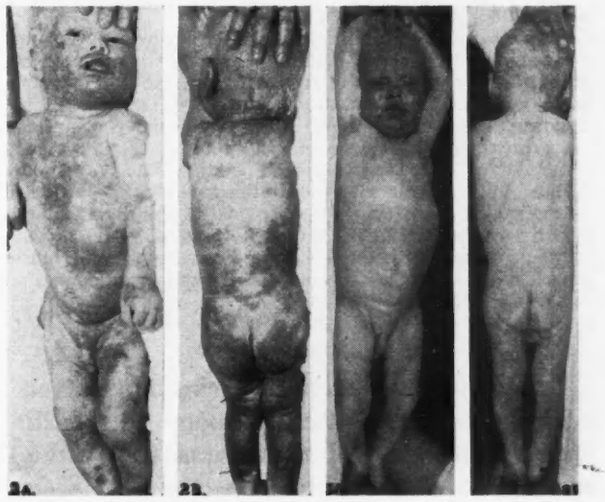
CASE REPORT

D.S., a white male infant aged 14 months, has been under the regular pædiatric care of one of us (J.H.B.G.) since birth. The allergic conditions in the family are as follows: mother is subject to urticaria and maternal grandmother developed eczema at the age of 15, and also asthma and rheumatoid arthritis at the age of 27. Patient's father is subject to bouts of allergic sinusitis and hand eczema, the father's brother suffers from hay fever and his son from asthma.

Patient manifested a persistent infantile eczema and recurring bouts of asthma at the age of 3 and 12 weeks respectively. On July 18, 1949, at the age of 6 months, he was hospitalized at the Infant's Hospital because of a generalized eczema, marked œdema and inability to gain weight. Treatment in hospital resulted in the disappearance of the œdema and some gain in weight, but the generalized eczema persisted and he suffered recurring bouts of asthma complicated by episodes of bronchopneumonia. He apparently is allergic to beef, egg, pablum and wheat cereal, oatmeal and orange juice.

On October 17, one of us (B.K.), saw the patient in dermatologic consultation and, when there was no apparent improvement following treatment with various therapeutic measures, suggested the experimental use of ACTH. The child was therefore transferred to the Vancouver General Hospital on December 21, so that careful studies could be carried out by the chemical pathologist (J.E.) and he was under the constant watchful care of the group including the endocrinologist (J.M.).

The clinical picture prior to ACTH therapy was one of a generalized eczema as illustrated in Fig. 2, and although the patient had no asthma his breathing was



Figs. 2a and 2b.—Showing widespread generalized eczema which had persisted and remained stationary for seven months: before treatment with ACTH.
Figs. 3a and 3b.—Taken on February 17, the final day of the second course of ACTH.

noisy. ACTH therapy was commenced on January 10, 1950, 10 milligrams dissolved in triple distilled water being injected intramuscularly every 6 hours for 48 hours and then every 8 hours, etc. (Fig. 1). Within 24 hours, there was a definite and marked improvement of the skin condition and after 48 hours of therapy there was virtually complete involution of his eczema. Within another 48 hours the expression and attitude changed from those of an anxious frightened child who was consistently indifferent to his feeding to a more assured and happy one who showed a marked interest in his surroundings and diet. On January 20, while still on ACTH there was a slight exacerbation of the eczema on his face and breathing became stertorous and wheezy. By January 22, there developed a persistent rise in temperature to 101° F. and he became restless with a troublesome cough. On January 24, the ACTH was stopped because of the persistent elevation of temperature, progressive difficulty in breathing, gain in weight, increasing cough, spread of the eczema and apparent distress of the child, which we feared could be evidence of excessive retention of fluids and electrolytes from over-stimulation of the gland with possible localized œdema of the lungs. On this date the serum potassium, sodium and plasma chlorides, were not grossly abnormal. X-ray examination of his lungs was suspicious of beginning pneumonic involvement of the right lower lobe and bacteriological cultures taken from the pharynx revealed the presence of pneumococci Type III, hæmolytic staphylococci and streptococci. He was then placed on aureomycin. Twelve hours following withdrawal of ACTH the temperature rose to 105°, and he had increasing difficulty in breathing, became cyanotic

* Bacteriologist, Vancouver General Hospital.

and his eczema became generalized. On January 29, the child presented the clinical picture of chicken pox (varicella) which was corroborated by the presence of other cases in the ward.

Upon recovery from chicken pox the eczema remained widespread but was less extensive than previously, so intramuscular injections of 10 mgm. ACTH were given every 6 hours from February 13 until the supply was exhausted on February 17. The response, although still striking, was not as complete as with the first course. The infant was able to be discharged home on February 18, with residual evidence of eczema on his scalp, neck and legs only (Fig. 3). It was noted that 10 minutes after each ACTH injection, the child became pale and listless and his colour and tone did not return to normal until some 30 minutes later. Also a transient abdominal distension followed each injection. The ACTH Lot H-7811 used in this case contained 1.0 units of pressor per vial and 0.15 units of oxytocin in the vial and the reaction to the ACTH injection in our case is clearly an oxytocin effect.

Within 3 days of his return home, a new eruption appeared on his face and shoulders and, within a week, it became generalized. This had a considerable element of a miliaria-like eruption and was evidence of an intolerance to the vegetable oil used for daily cleansing. At present, more than two months later, there is residual evidence of patchy widespread scaling and faint erythema, but there is an overall improvement despite the fact that he is cutting 4 teeth which normally is a non-specific cause for flaring infantile eczema. His breathing has remained normal except when he is emotionally upset, at which time it becomes noisy and is accompanied by coughing.

COMMENT

The atopic state includes such symptom complexes as atopic eczema (atopic dermatitis, infantile eczema and neurodermatitis) asthma and hay fever. In addition, migraine, urticaria and some gastro-intestinal manifestations should be included. These symptom complexes are produced, according to our present concept,[5] by an increased vascular permeability of the involved susceptible tissues. There is a definite hereditary predisposition and a family history is almost invariably positive for at least one of the atopic conditions. An increased eosinophil count is a frequent finding.

The allergic reaction is believed to be on a cellular basis. Specific antigens react with specific cellular antibodies, resulting in injury to the tissue cells with the liberation of an "H" substance (histamine-like). The release of this substance is thought to be initiated by stimulation of the parasympathetic nerves. It is the accumulation of histamine in susceptible tissues which produces the clinical syndrome by its pharmacologic effects. In the lungs, it may produce asthma, in the nasal mucosa rhinitis, and in the skin atopic eczema.

It is a universal experience in the management of these trying conditions, that factors other than specific allergens may be responsible for exacerbation of the symptoms. Unrelated non-specific factors such as cold, heat, infection, fatigue, teething and emotional stress have all been regarded as "non-specific" exciting agents. These factors have recently been re-assessed by Rackemann[6] in regard to asthma.

It was impossible to understand how such a variety of factors could produce a single identical symptom complex until Selye[7] introduced his theory of adaptation in which he showed that these stimuli all acted to produce a non-specific alarm reaction to which the normal individual subsequently developed a resistance. This resistance[7 to 10] was brought about by the production of excess ACTH by the anterior pituitary, which, in turn, stimulated the adrenal cortex to hyperfunction. With the absence of an adequate response by the pituitary or by the adrenal, a resistance failed to develop. Rose and Browne[11] showed that histamine metabolism was interfered with in adrenal failure and that injected histamine was not destroyed at the normal rate and so accumulated in the tissues.

Hence it may be that in the atopic state we are dealing with both a specific allergic reaction as evidenced by the exacerbation of symptoms upon ingestion or inhalation of specific antigens, and also with a disturbance in the reaction of the organism to changes in the external and internal environment as outlined by Selye in the alarm reaction.

Furthermore, as the hereditary influence appears to be important in atopic individuals, we can further speculate that there is an inherited endocrine deficiency or imbalance leading to an impairment of their ability to inactivate histamine. This results in the periodic accumulation of histamine in susceptible tissues, such as lungs, antral mucosa and skin with the resultant clinical syndromes. This impairment of function can apparently be restored to normal during the administration of ACTH.

Comment on laboratory findings and dosage.— During the control periods the number of circulating eosinophils at 2.00 p.m. tended to be increased over those enumerated at 8.30 a.m. (Fig. 1) but immediately treatment was instituted a rapid and absolute diminution occurred. This change persisted during the administration of ACTH, thus indicating that the functional reserve of the adrenal cortex was adequate.[12]

The fasting blood sugar varied within the accepted normal range during the first course

of ACTH therapy but was elevated on two occasions during the second course of treatment, suggesting some temporary hyperadrenalism.[13]

The blood urea nitrogen concentration was increased when the initial therapy commenced, and remained elevated until the day before this course terminated, when it approached the upper limit of normality.

The urine showed no protein, reducing substances, or ketone bodies during the periods of observation and treatment. The urea, uric acid and creatinine concentrations varied in the specimens tested and no consistent alteration was noted in the uric acid-creatinine ratio in the urines obtained before and after the 9.00 a.m. injection of ACTH. On the day before the first course of treatment was discontinued, a decreased sodium (133 m.eq/l.) was the only abnormality detected in the blood.

On culture, the pharyngeal swabs yielded moderate growths of coagulase positive, penicillin-resistant staphylococci and B hæmolytic streptococci, and a light growth of Type III pneumococci. In addition to being resistant to 2 μg./ml. penicillin, the staphylococcus was only sensitive, *in vitro,* to a concentration of 10.0 μg./ml. aureomycin. The other organisms were sensitive to less than 0.1 μg./ml. penicillin. It is possible that the administration of ACTH increased the child's resistance to this combination of virulent organisms, and may explain the further rapid rise in temperature and aggravation of all symptoms immediately following the withdrawal of the drug.

During the first two days of treatment 10 mgm. ACTH were administered every 6 hours and then the dose was reduced to 10 mgm. every 8 hours for the next four days. As the clinical improvement was so marked, on January 16, the dose was further reduced to 5 mgm. every 6 hours and, from the 18th, to 5 mgm. eight hourly. After this latter regimen had been instituted for 48 hours there was a slight elevation of the early morning temperature and some reappearance of symptoms, so the amount was increased to 10 mgm. ACTH twice a day for the next two days, and then to 10 mgm. every eight hours. The clinical condition continued to deteriorate and after administration was discontinued at 1.00 a.m. on January 24, the temperature increased markedly. It appears that whilst receiving ACTH the patient was better able to handle the infection he was developing, and it is probable that this may have been aborted had the dose been further increased. In spite of the fall in circulating eosinophils being maintained, the recrudescence which commenced on January 20 suggests that the previous dosage had been insufficient but, as the patient's weight was under 6.5 kilo., it is more likely that the interval between the injections was too long. During the course of therapy placebo injections failed to produce the clinical "side effects" noted with ACTH, and it is felt that these were attributable directly to the batch of ACTH being used.

SUMMARY

1. The treatment with ACTH is reported of an infant aged 14 months who suffered from generalized atopic dermatitis and recurring asthma.

2. During administration of ACTH there was a rapid and dramatic recovery of the eczema.

3. These diseases tend to recur when therapy is discontinued, but in this case considerable clinical improvement is still evident after 8 weeks.

4. Transient intense pallor, listlessness and abdominal distension were the only clinical "side effects" noted and they followed each injection of ACTH but not placebo injections. The youngster was highly sensitive to the oxytocin contaminant in the hormone.

5. The laboratory investigations confirm that ACTH can stimulate a dramatic decrease in circulating eosinophils and suggest that the amount administered to this case was insufficient to produce undesirable "side effects".

Appreciation is expressed to Miss K. Hoskins of the X-ray Department of the Vancouver General Hospital, for the illustrations.

Pituitary adrenocorticotropic hormone (ACTH) used in this case was generously supplied by Dr. John R. Mote of the Armour Laboratories, Chicago.

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ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS*

Harold Orr, F.R.C.P.[C.], F.A.C.P.

Edmonton, Alta.

THERE are four types of lupus erythematosus: (1) Chronic discoid. This includes the well-known "butterfly" lupus and is never fatal. (2) Chronic disseminated. This is an extension of the chronic discoid from the face to other parts of the body. (3) Subacute disseminated. (4) Acute disseminated. This is a systemic disease predominantly affecting young women, rarely occurring before puberty and only occasionally after the menopause. The cause is not known; there has been no satisfactory treatment for it, and it is invariably fatal.

The difference between subacute and acute disseminated lupus erythematosus is one of degree and is based on laboratory findings such as leukopenia, an increased sedimentation rate, a reversal of the albumin-globulin ratio, a reduction of the platelet count, and albuminuria.

Duff,[1] reviewing the work of Klemperer, Pollack and Baehr,[2] discussed their concept of a group of diseases involving fibrous connective tissue. The group includes lupus erythematosus, diffuse scleroderma, dermatomyositis, Buerger's disease, rheumatoid arthritis, periarteritis nodosa, acute rheumatic fever, sulfonamide and other drug sensitivities, and serum sickness.

Duff succinctly says, "The same pathological theme runs through all of them, but the variations on the theme are distinctive for each". For example, in lupus erythematosus fibrinoid necrosis dominates the picture. In acute rheumatic fever proliferative and inflammatory responses predominate, although fibrinoid necrosis does occur in the centre of the granulomatous reaction in the myocardium, producing the Aschoff nodule. Diffuse scleroderma is at the other end of the scale with a proliferative reaction producing quantities of dense collagenous connective tissue but an almost complete absence of necrosis and inflammatory reactions.

Collagen, as shown by Wolbach,[3] has its origin in an extracellular ground substance secreted by fibroblasts. It has the widest distribution in connective tissue fibre and is made up of broad wavy bands of many fibrils bound together by cement substance and has great tensile strength. When hydrated it becomes gelatin.

The idea that this syndrome is an allergic manifestation of tuberculous infection is a view no longer held. Kiel's[4] exhaustive study led him to the conclusion that the occurrence of tuberculosis in cases of lupus erythematosus is coincidental and unrelated. In England the theory is widely held that the streptococcus is responsible for most cases. On this continent there is a fairly general belief that the disease is the result of a response in a predisposed person to one of a variety of harmful agents. This is in agreement with Bloch's dictum that the type and course of the allergic reactions are independent of the nature of the antigen but vary according to the localization of the antibody. In acute disseminated lupus erythematosus, according to this concept, the antibody is concentrated in fibrous connective tissue and various antigens have been suspected, including the hæmolytic streptococcus, pneumococcus, gonococcus, tubercle bacillus, staphylococcus and foreign serum. Generich[5] believes that the sensitizing substance originates in the lymph nodes as the result of an unknown disease. Photosensitivity has long been regarded as a factor, due, it is suggested, to some product of metabolism such as hæmatoporphyrin, tyrosine, and other chemical substances known to produce photosensitiveness. Curtis[6] recently studied a patient with disseminated lupus erythematosus by determination of the leukopenic index after exposure to ultraviolet irradiation. The leukocytes fell from 6,500 to 3,000 and then, with the development of the erythema, went to 9,500 and fell to the normal level in a twenty-four hour period. This, he suggests, is an allergic reaction to light. It should be remembered, however, that, as pointed out by Selye,[15] tissue damage from a variety of causes such as, exposure to cold, burns, solar rays, x-rays, operative procedures, bacterial toxins, severe muscular exercise or treatment with various drugs and tissue extracts may cause a similar chain of events. This is the alarm reaction of the general adaptation syndrome and is distinct from the de-

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velopment of allergic phenomena elicited by micro-organisms or foreign proteins.

Klinge and Vaubel[7] demonstrated similarities between the pathological findings in lesions of the collagen group and lesions induced experimentally in animals by the administration of foreign proteins and their observation gave origin to the idea that these diseases are due to tissue hypersensitivity.

There are many observations which lend support to this view and the pathological findings in disseminated lupus erythematosus are described in several papers as being entirely compatible with those of allergic inflammation.

TABLE I.

ANALYSIS OF 154 CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS (UP TO 1938)

Data	*Type of disseminated lupus erythematosus*		
	Chronic (80 cases)	*Subacute (44 cases)*	*Acute (30 cases)*
Women, per cent	61	80	77
Onset as discoid type, per cent	60	34	33
Average age at onset, years	32	30	21
Average age at onset of dissemination, years	39	38	28
Lesions of mucous membranes, per cent	18	23	43
Prodromal symptoms, per cent	5	27	33
Sensitivity to light, per cent	22	23	23
Arthralgia or arthritis, per cent	20	57	63
Fever, per cent	5	57	97
Anæmia (less than 4,000,000 erythrocytes per c.mm. of blood or a concentration of hæmoglobulin of 70% or less), per cent	20	52	84
Leukopenia (less than 4,500 leukocytes per c.mm.), per cent	22	43	71
False-positive flocculation or Wassermann reaction, per cent	6	11	17
Renal irritation, nephrosis or nephritis, per cent	3	18	32
Infected tonsils, per cent	68	54	40
Deaths attributable to the disease, per cent	8	47	100

Because of the occurrence of the acute type in women during the child-bearing period of life, it has been suggested by Rose and Pillsbury,[8] and others, that an endocrine imbalance may be a factor. However, O'Leary states that therapeutic castration of women who have disseminated lupus erythematosus is valueless. Baehr states that treatment of disseminated lupus erythematosus with testosterone propionate or castration in women has not materially altered the course of the disease, and that he had not seen any evidence of endocrine disorder in men having disseminated lupus erythematosus. He thinks that the predominance of the disease in women represents a sex predisposition similar to the predisposition for men seen in thrombo-angiitis obliterans.

Hyaluronic acid is the major constituent of connective tissue which is not a stable, unchanging tissue but is a permeable network, the degree of permeability being affected by a variety of substances. One of these, the enzyme hyaluronidase, is found in testicular extract and increases the permeability. Corpus luteum does the same, but œstrogenic substances have the opposite effect. Cortisone and anterior pituitary adrenocorticotropic hormone (ACTH) will be discussed later.

In spite of the evidence that is piling up in support of the allergy hypothesis, one feels more and more that in some not yet fully understood imbalance among these hormones and enzymes lies the secret of the etiology of disseminated lupus erythematosus. Nothing, however, has been proved and we must continue for the time being to regard the cause as unknown.

Although connective tissue anywhere in the body may be affected, the cardiovascular system is involved so constantly that the disease has for long been regarded as a diffuse vascular disease. In the heart the most striking lesion is found in the endocardium and was first described by Libman and Sacks.[9] It was found in 30% of the material of Klemperer *et al.*[2] and is described by them as a dry granular pink vegetation varying in size up to 4 mm. in diameter and situated on the valvular and mural endocardium. The vegetations which consist of altered tissues are not merely laid

down on the endocardium. The process begins in the connective tissue beneath the intact endocardium and the growing mass of ground substance becomes grossly evident as the verruca protrudes on the surface. Actually, it may erode through the endocardium. Capillaries invade the verruca from below but are not numerous. At this time fibrosis is initiated and the lesion contains a few capillaries, fibroblasts, lymphocytes and some plasma cells. Newly formed collagen may in its turn suffer the same fate as the original connective tissue. The lesion now is a form of chronic granuloma and is practically always a mature neutrophilic polymorphonuclear leukocyte possessing a round vacuole containing partially digested and lysed nuclear material. This phenomenon seems to be due to material in the plasma of patients with disseminated lupus erythematosus. These investigators[11] put into plasma obtained from patients with disseminated lupus erythematosus, bone marrow obtained from patients who had various other diseases. The preparation was incubated at body temperature for a short time and then showed typical lupus erythematosus cells. The authors believe that

TABLE II.

ANALYSIS OF 132 CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS (1938 THROUGH 1947)

Data	*Type of disseminated lupus erythematosus*		
	Chronic (23 cases)	*Subacute (77 cases)*	*Acute (32 cases)*
Women, per cent	83	87	91
Onset as discoid type, per cent	30	17	6
Average age at onset, years	33	35	27
Average age at onset of dissemination, years	34	36	28
Prodromal symptoms, per cent	5	14	41*
Sensitivity to light, per cent	56	40	22
Arthralgia or arthritis, per cent	43	71	91
Anæmia (less than 4,000,000 erythrocytes per c.mm. or less than 12 gm. hæmoglobin), per cent	35	54	91
Leukopenia (less than 5,000 leukocytes per c.mm.), per cent	30	67	81
False-positive flocculation or Wassermann reaction, per cent	17	25	44
Renal irritation, nephrosis or nephritis, per cent	39	69	100
Albumin	39	56	100
Erythrocytes	9	34	81
Casts	4	17	69
Deaths attributable to the disease, per cent	4	35	84†

*Five patients had no cutaneous lesions when first seen here (lupus erythematosus without cutaneous lesions).

†Five patients were still alive at last report. One had completely recovered, having been followed for five years with no evidence of the disease for eighteen months. One was a semi-invalid followed for thirteen and one-half years after the onset of disease, seven and one-half years after dissemination. Efforts to follow up 3 patients were unsuccessful, and the chances are that these persons are dead.

and is apparently receptive to the implantation of bacteria. This occurred in four of the twelve cases in the series of Klemperer *et al.*,[2] in which endocardial involvement was found. Changes in the connective tissue of a similar nature, though often with very little inflammatory reaction, may occur in muscular arteries and connective tissue everywhere—especially in the kidneys, pericardium, pleura, peritoneum, skin and joints.

Hargraves, Richmond and Morton[10] about 18 months ago described a hitherto unobserved phenomenon in bone marrow preparations from patients with acute disseminated lupus erythematosus. The cell is present in about one-half the cases of acute lupus erythematosus their observations add weight to the hypothesis that acute disseminated lupus erythematosus is a result of hypersensitivity. For practical purposes the presence of this cell is pathognomonic, as it is not found in scleroderma, periarteritis nodosa and the other members of the collagen group. It has been found in multiple myeloma and in Hodgkin's disease.

Nearly half of the patients have prodromal symptoms of arthralgia often affecting the large joints. There is no roentgen evidence of bone change and the overlying skin is not reddened, but sometimes there is effusion into the joints. During the succeeding weeks or months there gradually develops a feeling of weakness, of being unwell. This may be accompanied by

the skin eruption which often, but not always, occurs first on the face and usually is erythematous in character. The eruption may extend to other parts of the body or may have begun on other parts and may be scanty or profuse, or, indeed, there may be no cutaneous signs at all. Sometimes it simulates erythema multiforme or erysipelas or an exudative dermatitis and may be hæmorrhagic. Erythema of the finger tips is characteristic. Fever develops and is persistent, sometimes low grade and often of the septic type. Albuminuria is a uniform finding, the kidney damage ranging from mild renal irritation to severe glomerular nephritis with the so-called "wire loop lesions" in the kidneys. The blood platelets are reduced, usually being below 100,000. The sedimentation rate is markedly increased, being above 60 mm. per hour in 80% of cases. Secondary anæmia is frequent. Leucopenia is a striking feature present in more than 80% of patients and occasionally dropping below 1,000 cells per cubic mm. The granulocytes suffer most, while the lymphocytes are more resistant so that a relative lymphocytosis may result. In a small percentage of patients, however, there is a moderate leucocytosis with no leucopenia at any time throughout the course of the disease. As in any other systemic disease, not all organs nor the same organs are affected in every case. The albumin-globulin ratio tends to reversal in nearly every patient and this is reflected in a high percentage of positive serologic tests—44% in Montgomery and McCreight's series.[12] Disseminated lupus erythematosus must therefore be listed with the diseases causing false positive serologic reactions.

The disease, as pointed out by Templeton,[13] is one in which there is tissue œdema, and sometimes acute abdominal pain indistinguishable from "surgical abdomen" occurs: knowledge of this possibility may obviate a surgical operation. For the same reason there may be symptoms referable to the central nervous system—even convulsions and coma. Then, of course, there may be endocarditis and pericarditis sometimes with pericardial effusion. Ocular symptoms have been noted, mostly affecting the retina. Lymphadenitis occurs and the spleen may be enlarged. Blood cultures are usually negative, but streptococci may sometimes be found in the terminal phase of the disease. Blood cultures have been positive, too, in some of the cases in which the abacterial verrucal endocarditis of Libman-Sacks became converted to bacterial endocarditis. The disorder waxes and wanes over a period of a few months to a few years. During the remission the patient may seem to be almost well, the cutaneous lesions may disappear, the temperature return to normal and the other general symptoms improve. Sometimes, however, the first acute attack terminates fatally without a remission.

TABLE III.

ANALYSIS OF OTHER LABORATORY DATA IN 132 CASES OF DISSEMINATED LUPUS ERYTHEMATOSUS (1938 THROUGH 1947)

	Type of disseminated lupus erythematosus					
	Chronic		*Subacute*		*Acute*	
Data	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Sedimentation rate, mm. per hour	20		70		31	
Normal, 0 to 20		35		14		0
Mildly increased, 21 to 40		25		16		3
Moderate, 41 to 60		25		21		19
Rapid, 61 or more		15		49		78
Serum Proteins (total)	2		33		22	
Normal, 6 to 8 gm. per 100 c.c. serum		50		79		64
Total proteins, less than 6 gm. per 100 c.c. serum		50		6		32
Total proteins, more than 8 gm. per 100 c.c. serum		0		15		4
Albumin-globulin ratio	2		31		18	
Normal, 1.5:1 to 3:1		50		16		6
Ratio less than 1.5:1		50		84		94

Since the appearance of the erythema may be late or may not occur at all, can the disease be diagnosed in its absence? O'Leary[14] states that a diagnosis of disseminated lupus erythematosus is warranted in the absence of cutaneous signs in a young woman with pains in the joints without roentgen evidence of bone change, a mild degree of fever, a high sedimentation rate and a leucopenia. If there is also present a reversal of the albumin-globulin

ratio, a reduced platelet count, albuminuria, anæmia, and the lupus erythematosus cell can be demonstrated from the bone marrow, the diagnosis is certain.

Aside from avoidance of exposure to sunlight, rest and supportive measures as found necessary, there was no treatment used up to a few months ago that would materially affect the course of this disease. Gold salts, bismuth and other remedies, useful in the chronic discoid type of lupus erythematosus, are harmful. Tocopherols have not helped. Surgical interference of any sort should be avoided. The extraction of a tooth may cause a serious exacerbation, and so slight an injury as that produced by an intramuscular injection may result in a reaction of the skin at the site of injection. New ideas in treatment should be tried, however, as in this way something useful may be found.

This brings us to the consideration of cortisone and one is hopeful that some form of cortisone therapy may prove to be the answer. It is too early to form an opinion because only a very few patients have been treated. Montgomery[16] stated in discussion that Brunsting had treated three patients with cortisone and one with ACTH and was of the opinion that these hormones might be of definite value in the treatment of disseminated lupus erythematosus, but too few cases had been studied to make a definite statement.

More recently, the Peter Bent Brigham Hospital group[17] have reported on the effect of ACTH administered to three patients with acute disseminated lupus erythematosus. This acts by inducing the secretion of substances similar to cortisone by the patient's own adrenal glands. All three patients, when given 10 mgm. of ACTH intramuscularly every six hours, showed marked clinical improvement with rapid disappearance of the typical rash; but five days after discontinuation of ACTH therapy the characteristic leukopenia, increased sedimentation rate and enlarged spleen returned. The treatment led to striking temporary improvement and left the patients in a better clinical state but did not lead to a cure. Two subsequent courses of ACTH therapy following partial regression in one patient showed beneficial effects lasting up to six weeks.

In December, 1949, through the courtesy of Dr. Baehr I had the privilege of seeing two patients currently being treated with cortisone at the Mount Sinai Hospital in New York. One of the patients improved dramatically in a few days from an almost moribund state to apparent good health on 200 mgm. of cortisone daily. On the eleventh day of treatment she developed moderate œdema and had gained ten pounds in weight, due largely to water retention. The blood sodium was elevated. Cortisone therapy was stopped abruptly and in forty-eight hours the patient had relapsed to where she was at the beginning. Cortisone treatment was resumed, giving only 100 mgm. daily. At the end of thirty days (the day I saw her) the sedimentation rate was 110 and the lupus erythematosus cell was present, but she was otherwise normal. The white blood count had increased to 6,500 from 2,000 and the platelets to 210,000 from 50,000. The albuminuria had practically disappeared, there was no arthralgia, the temperature was normal, and there was a slight rise in the blood pressure. The patient was up and about and stated that she was enjoying normal health. The other patient had also made a dramatic recovery. She was up and about and felt perfectly well. The lupus erythematosus cell was still present, but in this case the platelet count had remained low while the sedimentation rate had returned to 13 from 100.

It is apparent that one can hardly be accused of undue optimism in stating that the horizon is brightening and there is now a glimmer of hope for patients with this heretofore uniformly fatal malady.

We have prepared an analysis of our own 14 cases of acute and subacute lupus erythematosus, but we felt that the series is too small and there is not sufficient laboratory data on the earlier ones to illustrate adequately the significant points. So, with the concurrence of Dr. Hamilton Montgomery of the Mayo Clinic, his and Dr. McCreight's[12] analysis of 121 subacute and 62 acute cases is presented. This is the largest series of disseminated lupus erythematosus patients ever studied by one group of observers and constitutes one of the most exhaustive studies of its kind to be found in the literature. The tables are self-explanatory and bring out graphically the characteristic features of this disease.

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HERNIATED INTERVERTEBRAL DISC—A SURVEY OF POSTOPERATIVE RESULTS

H. H. Hepburn, M.D.

Edmonton, Alta.

THE main purpose of this article is to record the postoperative results of 220 cases of protruded, or herniated, intervertebral disc from the viewpoint of the patient. A questionnaire (Table I) was sent out from the office of the Superintendent of the University Hospital to 220 patients operated upon during the period from 1937 to 1947, inclusive. In order to encourage free expression of opinion, my name did not appear in the questionnaire. No cases operated upon since 1947 were included as it was thought that at least one year should elapse before the patient's personal reactions might be considered as crystallized. Of those who took the trouble to comment upon this point, a few reported finality in six months from the date of operation, but the great majority reported a period of resolution of at least one year, and quite a few said two years. No one claimed progressive improvement after two years.

TABLE I. (QUESTIONNAIRE)

UNIVERSITY OF ALBERTA HOSPITAL, EDMONTON, MAY, 1949

Dear Sir or Madam:

A copy of this letter is being sent to all persons who have had an operation for protruded, or ruptured, intervertebral disc in the University Hospital. The only purpose of the letter is to find out how successful the treatment has been. If you will be good enough to answer the following questions and return this form in the enclosed envelope, it will be a great help to us and to others.

1. Have you had another operation on your back in any other hospital since?
2. If so, what kind of operation?
3. Have you been able to do full work you were doing before operation?
4. Are you doing the same work but restricting or reducing it?
5. Are you doing a lighter type of work?
6. Are you unable to do any work?
7. Do you have severe pain?
8. Do you have slight pain?
9. Do you still have any numbness?
10. Do you have any weakness or paralysis?
11. What percentage of disability do you think you have? 0, 10, 25, 50, 75, or 100%?

This report is based upon the first 170 replies that came in. A few have come since but they do not materially alter the results. Table II gives an analysis of the type of patient included in the survey.

Table III gives the location of the lesion and the type of operation performed.

Table IV is compiled from the replies to the questions in Table I. It must be remembered that these are the replies and personal estimates of disability by the patient, and are not the result of medical examination. Some of these patients have not been seen by me for ten years and the majority not for at least five years, but,

TABLE II.

	1937	*1938*	*1939*	*1940*	*1941*	*1942*	*1943*	*1944*	*1945*	*1946*	*1947*	
Total number of cases	1	4	4	2	1	6	3	21	53	46	79	220
Male	1	4	4	2	1	6	3	13	44	34	63	175
Female								8	9	12	16	45
Age 1 to 20 years											3	3
20 to 30 "		1	2	1	1	1	1	5	20	10	22	64
30 to 40 "		2	1			2		9	19	18	29	81
40 to 50 "	1	1	1	1		3	1	4	9	16	18	54
50 to 60 "								3	3	1	6	13
60 to 70 "							1		2	1	1	5
History of severe injury	1					1		1	2	6	13	24
History of slight injury		3	2		1	4		8	12	10	27	67
No history of injury		1	2	2		1	3	12	39	30	38	129
W.C.B. or D.V.A	1	2	2		1	3			30	19	30	88
No compensation		2	2	2		3	3	21	23	27	48	132

TABLE III.

	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	
12D - 1L										2		2
1L - 2L											1	1
2L - 3L											1	1
3L - 4L									3		1	4
4L - 5L		2	2		1	1	1	2	19	21	34	83
5L - 1S		2	1	2		6	1	21	35	27	43	138
Right	1	1		1	1	1	2	12	29	19	30	97
Left		3	3	1		5	1	11	27	27	48	127
Ruptured posterior common ligament	1	4	1	1	1	5	1	13	29	28	50	134
Interlaminar operation							2	1	26	25	50	104
Partial or total laminectomy	1	4	4	2	1	6	1	20	27	21	28	115
Simple extraction of loose fragment		3	1		1	3		2	1		2	13
Curetting of disc	1	1	3	2		3	3	19	52	46	76	207
Re-operation on disc		1				1			4		3	9

judging from those I have re-examined in recent years, I would say that the estimation of percentage of disability is somewhat higher than I would place it. For example, one woman reported restricting her household work and gave a negative answer to all other questions, but estimated her disability at 50% of total.

The table below shows that, in the patient's own estimation, 72.35% have a residual disability of 25% or less; 66 patients were W.C.B. or D.V.A. compensation cases. Of these, 41, or 62.12%, claimed a disability of 25% or less, 25, or 37.87%, claimed a disability of 50% or over. All three claiming 100% were compensation cases.

As might be expected, those eligible for some form of compensation have estimated their disability somewhat higher than those not eligible for any form of compensation, as shown in the note at the foot of Table IV. In that connection, one must remember that the man eligible for compensation is probably not his own boss, and consequently his disability becomes a greater handicap than it would be if he were able to modify his work and protect himself. Nine of the 220 cases were known to have required re-operation in University Hospital at the same, or another level. Three additional cases reported having had another operation in some other hospital, one of them a spinal fusion. This makes a total of 12 out of 170 replies, or 7%, requiring a second operation.

TABLE IV.

		Percentage
Number of questionnaires sent out	220	
Number of replies received	170	77.0
Number already known to have had a second disc operation in the University Hospital	9	5.29
Subsequent operation on a disc	2	1.18
Subsequent spinal fusion	1	0.59
Total number having a second operation	12	7.0
Doing the same work as before	47	27.64
Doing same work restricted	82	48.23
Doing a lighter type of work	36	21.17
Unable to do remunerative work	3	1.76
Having constant severe pain	3	1.76
Having intermittent severe pain	44	25.88
Having constant slight pain	16	9.41
Having intermittent slight pain	94	55.29
Residual numbness or paræsthesia	105	61.76
Severe weakness of a limb	2	1.18
Slight weakness of back or of a limb	87	51.17
Patient's estimate of percentage of disability at 0%	31	18.23
10%	36	21.17
25%	56	32.94
50%	33	19.41
75%	9	5.29
100%	3	1.76

I am not in favour of immediate spinal fusion as a routine treatment for herniated, intervertebral disc, and recommend it only in the following three classes of cases: (1) where there is an unstable back due to developmental defect or fracture; (2) where myelograms show a bilateral, hour-glass type of filling defect at the 4L - 5L level, a class of case in which, in my experience, the conservative disc operation has been disappointing; (3) that small group of cases who are unable, or unwilling, to face a 7 to 10% risk of requiring a further operation.

Even if a patient is obliged to submit to two interlaminar disc operations. I doubt that the loss of time will be as great as that following immediate, spinal fusion. Even ardent advocates of spinal fusion must agree that one fusion operation is not a positive guarantee that no subsequent operation will be required.

I have heard the statement that patients will not return for another operation, given as a reason for doing an immediate fusion. This, in my opinion, is not a valid argument, nor is it strictly accurate.

One item that surprised me in the survey was the large number, 61.76%, who reported a persisting numbness or paræsthesia.

The majority of those who reported intermittent, severe pains, associated them with muscular cramps, usually nocturnal, aggravated by exertion and by exposure to cold. Fortunately, these painful cramps appear to be reduced in severity and in frequency in the course of a year or two, although some have persisted for several years.

One reason for this survey was to record information by which one might judge the relative merits of a simple disc operation as opposed to immediate spinal fusion. It would be of great value to have a parallel series of spinal fusions reported upon from the viewpoint of the patient.

Until it has been proved that spinal fusion will leave more than 75% of cases with less than 25% disability, it would appear reasonable to recommend the more conservative form of treatment.

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RÉSUMÉ

L'auteur a envoyé un questionnaire à tous les patients opérés pour hernie discale en s'informant des symptomes encore ressentis et de l'incapacité présente. 72% des patients (170) ont répondus à ce questionnaire. D'après les réponses l'auteur a conclu: (1) qu'il n'est pas nécessaire de faire une fusion au premier temps opératoire excepté pour des indications précises qu'il énumère. (2) qu'un très grand nombre de patients accusent encore des engourdissements (61%). (3) que les douleurs sous forme de crampes disparaissent en général, graduellement après un an ou deux. L'auteur suggère en terminant de faire une enquéte semblable auprès de ceux qui ont subi une fusion lors de leur opération.

YVES PRÉVOST

THE PRESENT STATUS OF THE MEDICAL TREATMENT OF HYPERTHYROIDISM*

D. M. Baltzan, M.D., F.R.C.P.[C.]

Saskatoon, Sask.

THE assignment to discuss this subject affords an opportunity to assess the present position in this period of revolutionary therapeutic advances.

THERAPEUTIC GRADING

Before treatment starts it is necessary to establish that the patient has hyperthyroidism, and that treatment for it is in the order of first magnitude. If hyperthyroidism is combined with other unrelated disease, treatment is dispensed in the order of merit. For instance, patients with hyperthyroidism who suffer more from independent migraine or essential hypertension may require a subtotal thyroidectomy; unilateral treatment will not produce a double cure.

Hyperthyroidism exists if excess thyroid hormone in the body results from hyper-functioning of the gland naturally or artificially induced, and the excess causes attributable disturbances. That is the critical decision which, for practical purposes, is all the diagnosis necessary to begin treatment. Some place emphasis on differences related to a diffuse thyroid gland hyperplasia, and to a nodular gland hyperplasia. The distinction is not of primary importance. If there is hyperthyroidism, treatment for it is based solely on overactivity at the point of toxicity. A much lobulated gland, a solitary cystadenoma, a "woody" thyroid gland, and suspected neoplasia, require treatment for different indications. On the opposite side mimic symptoms of other etiological origins must be carefully eliminated. The chief imitators are concealed pulmonary tuberculosis, undisclosed subacute bacterial endocarditis, primary arterial hypertensions and above all, anxiety neuroses, neurocirculatory asthenia, and sympathomimetic disorders.

The strategy of treatment will depend upon the amount of thyroid hypersecretion and intoxication. There are subacute manifestations of hyperthyroidism, acute thyrotoxicoses, and hyperthyrotoxicoses. Time does not permit describing in full the framework of the subclassification used to guide treatment. If basal metabolic rate figures were reliable indicators of all the clinical implications, categorically, plus 20 and under conforms to subacute thyrotoxicosis, plus 60 and under conforms to acute thyrotoxicosis; above this rate there is potential hyperthyrotoxicosis. Unfortunately, rules based on basal metabolic rate estimations alone are not definitive.

THERAPEUTIC TESTS AND RATIONALE

In indecisive cases, and in occult forms of hyperthyroidism, iodine is the simplest test drug when there is need for more proof. Iodine is selective in its action upon the thyroid gland, temporarily blocking the delivery of hormone from the gland. The newer anti-thyroid drugs are not as quick-acting, and it is suspected

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their pharmacologic actions are not restricted to the thyroid gland alone. Lugol's solution is given in 5 or 10 minims doses three times daily for ten days. The basal metabolic rate before and after this period is taken. In the end, even more emphasis is placed on the symptomatic response which follows. In borderline cases we frequently prescribe, for comparison, small amounts of phenobarbital in three divided doses daily for ten days preceding iodinization. It is then noted which one of the two test periods produced betterment.

Prior to 1923 providential remissions, x-ray irradiation of the gland, and hazardous surgery were all poor prospects for the sufferer. After Plummer introduced iodine medication the era of successful surgical treatment of thyrotoxicosis was to endure almost exclusively for two decades.

In 1943 the new epoch of medicinal antithyroid therapy started.[1] This was a tremendous practical advance. Until the cause of the accelerated activity originating in the romantic hypothalamic area is discovered, treatment can be rationalized along these lines; (*a*) suppression of the hypothalamic-pituitary stimulus by irradiation of the pituitary area when practical, (*b*) inhibition of thyroxin delivery by iodine administration with limitations; thyroid gland irradiation; surgical ablation and radioactive iodine, (*c*) reduction of thyroxin synthesis by thiocarbonamide chemicals, and (*d*) neutralization of thyroxin already formed, by an anti-hormone, which has yet to be effectively demonstrated.

Subacute Hyperthyroidism

It is well recognized that hyperthyroidism can be a cyclic disorder with periods of exacerbation and remission. The disease may resolve itself spontaneously and become inactive. Therefore, not infrequently, one feels challenged later with the accuracy of his first impressions. We have not had reason to abandon the custom of treating the disease in this mild phase with iodine plus collateral restoratives. The ban on the protracted use of iodine has been lifted by the hand of experience. Iodbasedow is a forgotten entity and iodine refractoriness is disputed. If the clinical response is satisfactory there are no lurking risks for this palliative program. There is no danger of insidious cardiac complications and there is no negligence in respect to the prevention of exophthalmos. Radical surgery is not a guarantee against the latter. On the contrary, the abrupt diminution of circulating thyroid hormone stimulates the production of thyrotropic hormone and releases without opposition the oculotropic factor.

Restorative measures include the reduction to the minimum of as many of the disturbing elements in the patient's environment as possible. A holiday is beneficial but it can be disturbing if it is not congenial. Freedom from fear is necessary. To this end avoiding the needless threat of an impending operation is preventative. Complete rest is not obligatory, only the amount of work must be limited. It is important to insist upon a greater protein diet with a high vitamin B content and a sufficient quantity of food to balance the hypermetabolism. Numerous prescriptions are costly, laborious, and perplexing. Economic compounding is rewarded by better co-operation.

Acute Thyrotoxicosis

In acute thyrotoxicosis the sinister signs are conspicuous and one or more of the well known cardinal features are evident. Hitherto, acute thyrotoxic patients were destined for surgical treatment. Now, patients are carefully screened for surgery. Acutely toxic patients who would profit best by cutting the period of toxicity to the shortest time, patients with partial results from anti-thyroid drug treatment and those who for expediency must have speedy action are all candidates for operative treatment. Complications such as auricular fibrillation with cardiac failure, for example, are not specific indications for this short-cut.

Preoperative medication. — The physician's function in connection with the surgical problem extends to the preoperative preparation of the patient. The program is undergoing some changes with the introduction of the newer drugs and the procedure is not yet standardized. Iodinization plus the usual adjuncts has in the past, with rare exceptions, always been dependable. Most clinicians prescribe propylthiouracil and begin iodine only two weeks preceding the contemplated date of operation. Others prescribe iodine and propylthiouracil simultaneously in all cases anticipating operation. It is advisable to discontinue thioureæderivative medications one week before the date of operation in case granulocytopenia should develop during the critical period, and

also because there is less likelihood of encountering acute myxœdema immediately following operation.

Propylthiouracil treatment. — As experience and confidence grows, the prospect for exclusive therapy is increasingly promising. Statistical evidence so far is no assurance in the individual candidate commencing treatment. The unpredictables are drug reactions, hazards during the time-lag before therapeutic response is elicited, and the length of time treatment will be required to bring about a lasting remission. Propylthiouracil has diminished many of the uncertainties accrued through the earlier experiences with the use of thiouracil. Reactions are so uncommon with propylthiouracil as to justify ambulatory treatment. Hospitalization has, however, not been entirely eliminated in acute thyrotoxicosis. The average dose of propylthiouracil is about 200 mgm. per day. Amounts up to 300 or 400 mgm. may be necessary in severe toxicities. If propylthiouracil therapy is expedient, the initial dose should not be lower than 150 mgm. a day. Previous iodine medication is no hindrance except that the response is slower. Action is slower in large toxic nodular goitres because of excessive thyroxin storage which prolongs the symptoms of hyperthyroidism. To sustain the effects a maintenance dose is continued for some time after all the symptoms have disappeared. In the majority 75 mgm. per day is the estimated requirement, while only 50 or 25 mgm. a day may be sufficient for some individuals. An initial white blood count and differential count is a precautionary step. Repeated routine blood counts at regular intervals are not compulsory except in unfavourable turns of events.

In the first four weeks, after implementing propylthiouracil therapy, it becomes evident whether the response is encouraging. If progress is satisfactory there should be no need for a radical revision of the plan for three months' time thereafter. It is premature to appraise the adequacy of this treatment before this length of time. Lasting remissions require at least six to nine months' treatment. Relapses appear to depend on several conditions, namely, the initial severity of the disease, size of the thyroid gland, inadequacy of treatment, duration of treatment, and maintenance requirements. No definite statement can be made as to the time required to produce a persistent remission. If the disease is under control the time element is not sufficient reason to abandon drug therapy.

Supplementary treatment. — Conditions that lead to increased cellular metabolism tend to produce a thiamine deficiency. This deficiency seldom produces the complete thiamine deficiency picture observed in experimental thiamine deprivation. Some deficiency symptoms in experimental hyperthyroidism did not disappear completely after administration of thiamine alone but they disappeared on addition of pantothenic acid and pyridoxine.[2] Clinical signs of this failure in hyperthyroidism are not generally evident but should be anticipated by the administration of a vitamin B complex supplement.

Apart from supplying a high caloric diet and conserving energy while the thyrotoxic drain goes on, no other accessory treatment is usually necessary in the uncomplicated case. Coincidental situations such as climacteric disturbances, anæmic factors, diabetes, etc., must receive due attention.

Radioactive iodine. — We have not had first hand experience with the use of radioactive iodine. Iodine, which has been rendered radioactive and administered orally, is collected in the thyroid gland because the gland absorbs iodine selectively. In this form, a radiation effect is produced. The present status of the treatment indicates it should be administered under controlled conditions. It is an alternative treatment in patients who are sensitive to ordinary iodine or propylthiouracil, and who are poor operative risks. Its greatest use will probably be in carcinoma of the thyroid gland.

Guides in treatment. — Clinical criteria are sufficiently dependable without the necessity of frequent basal metabolic rate determinations and other special laboratory tests, to guide the course of treatment. The general well-being of the patient, increasing weight, declining pulse rate, along with observation of the size and vascularity of the thyroid gland are signposts. To maintain the proper level, a maintenance dose of propylthiouracil is administered, tapering off by degrees. Excessive dosage ushers in myxœdema. The forewarnings are lethargy, sluggishness, excessive gain in weight, and later, a puffy appearance of the face, and a conspicuous enlargement of the thyroid gland.

HYPERTHYROTOXICOSIS

Everyone is on the alert for postoperative thyrotoxic crises. Thyroid storms are precipitated otherwise, too. Intercurrent infections, the withdrawal of iodine medication, toxic psychosis, severe physical strain and trauma are occasional precursors. The syndrome is an augmentation of the symptoms of thyrotoxicosis, to an extreme degree. The majority of hyperthyrotoxic states occur in patients with thyrotoxicosis of relatively short duration. Many are too ill to have their metabolic rates determined. McArthur *et al.*[3] report the average rate of five patients who did not have surgery, was plus 70; the metabolic rate on admission of patients in whom crises developed postoperatively was plus 49. McArthur and associates[4] summarized the aims of treatment in these critical states as follows: (1) prevention of tissue anoxia by supplying continuous oxygen; (2) inhibition of the discharge of thyroid hormone from the thyroid by the administration of iodine; (3) suppression of the manufacture of new thyroid hormone by giving thiouracil; (4) protection of the liver by giving dextrose and vitamin B complex; (5) correction of abnormalities in electrolyte concentrations and in the volume of plasma and extra-cellular fluids; (6) compensation for possible adrenal exhaustion by the administration of the whole adrenal cortical extract; (7) limitation of infection by penicillin therapy and (8) reduction of the prolonged prothrombin time with vitamin K. These steps endeavour to correct all recognizable abnormalities stemming from the hypermetabolism.

COMPLICATIONS

Auricular fibrillation.—It is not clearly known whether thyroxin adds a degree of irritability to the muscle fibres, which causes them to fibrillate sooner than otherwise. Andrus[5] noted that auricular fibrillation with hyperthyroidism occurs only in patients over forty years of age or patients in whom the heart has suffered damage such as rheumatic endocarditis. The benefits obtained from digitalis are less pronounced than in other forms of auricular fibrillation. When simple tachycardia alone exists, the use of digitalis is without benefit. Quinidine is most valuable in obtaining reversion to normal rhythm in cases of auricular fibrillation which do not revert spontaneously after operation.

Progressive exophthalmos.—Ordinary exophthalmos is a part of the general clinical syndrome. Abolishing the thyrotoxicosis does not always take care of the exophthalmos. On the contrary, while the great majority appear to have a recession of the exophthalmos after a satisfactory subtotal thyroidectomy, careful observation of the eyes of these patients with exophthalmometer measurements made before and after thyroidectomy may reveal that the disappearance is misleading. With thiourea derivatives alone 10% of the patients showed a significant increase in exophthalmos compared with an incidence of 50 to 66% of exophthalmos after thyroidectomy, and an incidence of 20% of exophthalmos reported after roentgen therapy for thyrotoxicosis.[6] A slow return of the endocrine balance is conducive to lessening the tendency of exophthalmic occurrences. In the presence of pronounced exophthalmos, while controlling the liberation of thyroxin at the source, a level of artificial circulating thyroxin may be maintained as counter-balance by the administration either of thyroxin or thyroid extract.

Malignant exophthalmos.—This is an extreme protrusion of the eyeballs complicated by œdema and inflammation of the eyelids, and other local involvements which may lead to ulceration of the cornea and papillœdema, ultimately leading to complete destruction of the eye. There are thyrotoxicoses without eye involvements, and little or seemingly no thyrotoxicosis with eye involvements of this genesis. The consensus is that patients entering upon the hyperophthalmopathic phase should not be operated upon. They should be treated by non-surgical methods, namely, thiourea derivatives, roentgen therapy or radioiodine, plus the administration of thyroid extract. Irradiation of the pituitary area may help reduce the pituitary thyrotropic activities. Several surgical procedures for relieving the danger to the eyeball have been devised and are used in extreme cases.

Hepatic insufficiency. — Thyroxin depletes glycogen storage in the liver and was shown experimentally to cause damage to the liver tissue directly. Clinical evidence of disturbed liver function is recognized less than can be demonstrated by liver function tests. Prothrombin is commonly reduced. Occasionally, the impairment in liver function is so severe as to produce jaundice or precipitate a thyroid crisis.

Miscellaneous. — Diuresis, diaphoresis, and diarrhœa carry off much fluid. Dehydration must be counteracted. Pitting œdema sometimes develops in the course of treatment due to unopposed action of the water storage principle of the anterior pituitary hormone. Thyroid extract given during this time corrects the disequilibrium. Weakness, especially of the leg muscles, is common and there may be extreme myotonia. General weariness, aches and pains are due partly to the loss of calcium, and partly to the large excretion of creatine. Excessive loss of nitrogen, calcium and phosphorus is characteristic of thyrotoxicosis. Specific replenishments may be made but they are usually unnecessary because these factors are automatically adjusted when the thyrotoxicosis is controlled.

CONCLUSIONS

The better management of the hyperfunctioning thyroid gland has received renewed impetus, but there is not yet a fundamental solution. There is new fire-extinguishing material. There is no prevention and no means to eliminate entirely the ruins brought about. Always there are unexpected cross-currents. At this moment a hyperthyrotoxic case under treatment is saturated with iodine without attaining optimum control to make surgery safe; propylthiouracil suppresses her white blood count critically. Conversely, in another case of acute thyrotoxicosis the patient is allergic to iodine, and life-saving iodine in case of a postoperative crisis cannot be commandeered. In addition, she has asthma and cannot be given adrenalin.

Anti-thyroid drugs are converting many of the nodular toxic thyroids to a non-toxic state. The problem of dealing with non-toxic nodular goitres is therefore multiplying. In 2,000 consecutive routine physical examinations nearly 100 nodular formations were felt in the thyroid gland, the majority of which were entirely unrelated to any symptoms for which these patients were examined. The findings pertain to this territory. Will it be aggressive or wise to extirpate these and the newly converted ones? A concerted effort has to be directed towards some unanimity in the handling of these and the added numbers before superimposing iatrogenic suffering which is inevitable where conflicting opinions abound.

On the brighter side, it has been proved that surgery is safer than ever before by combined preoperative anti-thyroid drug and iodine preparations. Large series of cases are already being reported without a single mortality.[7] Other series of cases are on record where surgery has not been resorted to at all.[8] In a selected group of consecutive "thyroid" patients examined recently, the proportionate allocations were: 28 subacute thyrotoxicoses, 60 acute thyrotoxicoses, 3 hyperthyrotoxicoses (2 medical and 1 postoperative), 4 thyroiditis, and 1 malignancy. In a period of 5 years from 1944 to 1948 inclusive, in the surgical service of St. Paul's Hospital, thyroidectomies progressively declined by 40%. On the medical side our directive for interventions has, in the five year period, dropped 60%. Somewhere between the percentage of reduced surgical activities in the hospital and our figures, it would seem, is the correct position of the local reactions to the new turn of events. In this transitional period, the number of operations for acute thyrotoxicosis and hyperthyrotoxicosis has obviously declined sharply. This trend is a good portent for the future. What the remissions which we count on will do to alter the statistics either way, more time and experience will tell.

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402-408 MacMillan Bldg.

RÉSUMÉ

L'auteur constate qu'il y a eu plusieurs améliorations au traitement d'une thyroide hyperactive mais que cependant la solution fondamentale manque encore. Il n'existe pas de moyens de prévention, souvent des patients saturés d'iode ne sont quand même pas controlables pour la chirurgie, on a rapporté fréquemment des complications à la suite de l'emploi du propylthiouracil. De plus l'hyperthyroidisme dans plusieurs cas s'accompagne de maladies concomittantes qui le rendent difficiles à soigner. Les médicaments anti-thyroidiens transforment de nombreux goîtres nodulaires toxiques en non-toxiques. Le problème se pose alors de savoir quoi faire avec ces lésions. Doit-on les extirper ou non?. La chirurgie est maintenant beaucoup plus sure qu'elle ne l'était à cause de la préparation pré-opératoire. Cependant la tendance actuelle est à la prépondérance du traitement médical. Il est difficile de prévoir le traitement futur de l'hyperthyroidisme, seulement le temps et l'expérience nous le diront. YVES PRÉVOST

THE SURGICAL TREATMENT OF MITRAL STENOSIS

Gordon Murray, M.B., F.R.C.S.[C.& Eng.]

Toronto, Ont.

MITRAL stenosis has been considered to be a medical disease, and the treatment was purely symptomatic, designed to assist the damaged muscle, to overcome the obstruction produced by either the regurgitation or the stenosis or both. The cardiac failure appearing later in the disease, was treated by rest and various drugs. However, the pathological lesion, namely the stenosis, was unaffected by such treatment and its course in many cases was that of progressive narrowing of the opening until the obstruction was responsible for complete failure of the circulation.

Since MacKenzie's time, it has been thought that the state of the musculature was more important than was the state of the valves. However, it must be obvious that if the muscle is damaged, the presence of an obstruction is of greater importance than if the muscle is not damaged. Ultimately the obstruction may reach a point where, no matter what the state of the muscle, failure of circulation ensues.

Attempts have been made by many investigators to try to relieve the state of affairs caused by the obstructing valves. The work of Samways,[1] Brunton,[2] Cushing and Branch,[3] Bernheim,[4] Scheppelmann,[5] Allen and Graham,[6] Cutler, Levine and Beck,[7], Pribram,[8] Souttar,[9] Allen,[10] Tuffier,[11] Doyen,[12] Powers,[13] Harken,[14] Carrel,[15] Haecker,[16] Bjork,[17] Shaw,[18] Templeton and Gibbon,[19] together with the more recent work of Cutler,[20] Smithy,[21] Bailey, Glover, MacNeil and Harken,* has all been designed to relieve the obstruction produced by the valve, hoping thereby to improve the condition of the circulation as a whole. My first attack on this problem was in the laboratory during 1936. The results of this were published in 1938.[22] With my assistants, Dr. Wilkinson and Dr. Ross MacKenzie, the posterolateral cusp of the mitral valve was resected, keeping away from the septal cusp and any possible injury to the bundle of His. In the control animals, when this alone was done, removing a large portion of the mitral valve, the animals showed signs of marked mitral regurgitation with dilatation of the left auricle and embarrassment of heart action within a short time, and only a few survived over night. When, however, to prevent the regurgitation after such a resection, we managed to insert a new valve satisfactorily, the animals stood the operation very well, did not show signs of regurgitation, and survived. The longest survivor was an animal who lived seven years following the operation, and died of old age, as no other lesion was found. During this seven years of life with the artificial valve in his heart, the animal was normal in all respects. He had plenty of energy, could scrap with the other dogs, and had good exercise tolerance. Following his demise, we recovered the specimen. This showed that a good portion of the postero-lateral cusp of the mitral valve had been resected, leaving a large opening. The newly applied valve was in good condition and was functioning well; it had not degenerated, there was no sclerosis of the surface, no thickening or hardening, no inflammatory changes, no thrombi, it was pliable and it seemed to be in good condition.

However, this was not applied to human beings until 1945.

In the meantime other investigators have continued to work on this problem, hoping to do something for the vast army of cardiac invalids resulting from the effects of rheumatic infection, appearing in commonest form in mitral stenosis, causing left auricular enlargement, perhaps going on to fibrillation and ultimately failure, with invalidism usually lasting for many years. Smithy,[21] a sufferer himself, took a keen interest in trying to develop some method of relief for such patients. He published his first paper on this subject in 1947, in which he planned to do a commisurotomy, hoping that by resection of what might be a rigid annular rim around the opening of the mitral valve, the remainder of the cusp might be flexible enough, that the stenosis might be relieved to a degree and regurgitation prevented. This operation was done, approaching through the left auricular appendage, or the left ventricle in some. Seven patients were operated upon with two deaths. There was clinical improvement in three. Some of these patients were able to become more active and showed less signs of failure. However, on the whole, one uncertain factor in the procedure was the possible regurgitation following the operation. Perhaps this depended to a degree on the pathology of the mitral valve itself.

* Personal communications.

Bailey, Glover and MacNeil of Philadelphia then took up this plan and devised an ingenious method of dividing the mitral valve, performing a commisurotomy, again approaching through the left auricle. This had the disadvantage, as had Smithy's[21] procedure, of great danger from leakage and hæmorrhage from the enlarged left auricle with its high continuous pressure and the thin wall which was difficult to handle in controlling hæmorrhage. However, they operated upon a moderate number of patients with improvement, but again the results were always qualified by the question of how much regurgitation occurred as a result of the operation designed to relieve stenosis.

Harken operated upon patients, again through the left auricular appendage with moderate success, but results were marked by some operative mortality rate from hæmorrhage from this thin-walled auricle with its high continuous pressure.

Another method of surgical treatment used by Sweet and Blalock was designed to relieve the left auricular pressure and thereby it was hoped to relieve the patients of some of the symptoms of pulmonary œdema, etc. This involved the formation of an interauricular septal defect, so that the left auricular pressure would be relieved by escape through this opening into the right. Another method with similar principles in mind was the anastomosis of one of the pulmonary veins to the vena azygos or other systemic vein thereby letting down the pressure in the left auricle. Both of these methods have produced some symptomatic improvement in some patients, but it obviously was not an entirely satisfactory method of relieving the situation as it produced only a vicious circle in the long run. Moreover, the venovenous anastomosis between the pulmonary vein and systemic vein was difficult to keep patent and it has been shown that a great number of these become thrombosed.

Based on my early experimental work,[22] I was satisfied that the procedure of division of the valve alone or of removal of a portion of it to relieve stenosis, would produce a variable amount of regurgitation and this was more important and dangerous than the benefits derived from relief of the stenosis. It was thought, therefore, that the method of removing a fair amount of the valve was important and that the application of a new valve was essential to prevent regurgitation. This work was based on the following principles.

1. The stenosis must be relieved, and removal of a portion of a stiff valve would provide better relief than would mere division of a similar stiff valve. The argument in favour of this is that if the valve is stiff, the difficulty of the thin walled auricle emptying through a stiff rigid valve slit is greater than is the regurgitation from the ventricle in its high pressure stage during systole.

2. If enough of the valve is removed, the stenosis may not recur. In experimental work on stenosed valves, if the valve is divided only, the disease and fibrosis which caused the stenosis and made it a progressive lesion, may heal up the slit in the valve and ultimately the stenosis is not relieved. If a portion of the valve were resected, this was overcome.

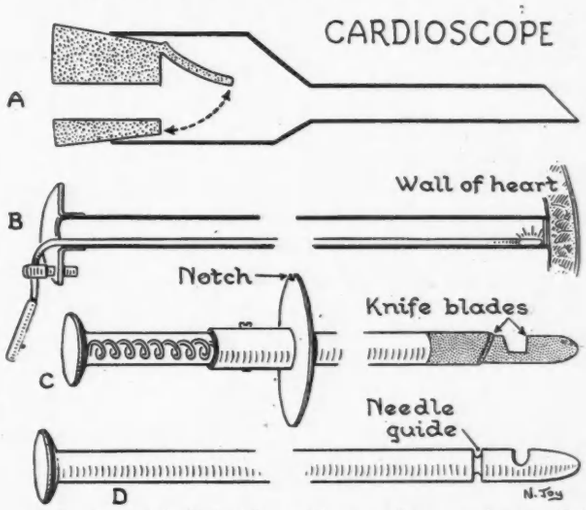


Fig. 1.—(A) Cannula with a rubber valve. (B) Cardioscope with a glass window on the end which is applied directly to the surface to be looked at, passing it through the cannula. (C) Punch or cardiac scissors which also passes through the cannula. (D) Guide which passes through the cannula and marks the site at which the new valve should be placed.

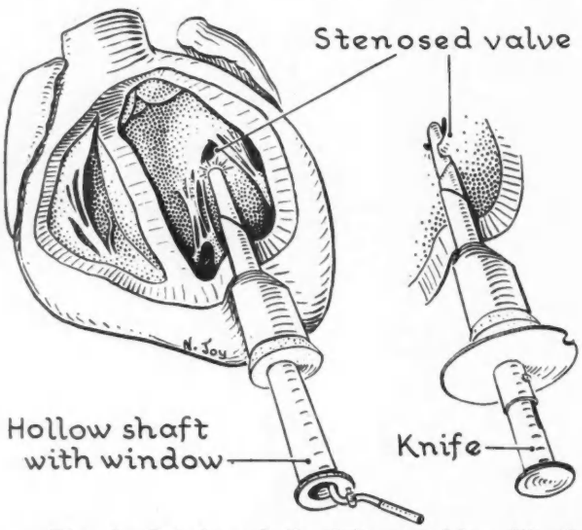
3. If the valve were resected, it was necessary to apply a new valve to prevent the regurgitation.

The type of valve used.—The valve must have the following qualities: (1) It must be flexible enough to obstruct the opening during systole, but must not obstruct the opening during diastole, so that it will not interfere with the filling of the ventricle. (2) The valve must be of such a quality that it can live within, and gain its nutrition from the blood stream. (3) It must be of such a substance that it will not cause clotting or thrombosis. (4) It must be of such texture that it will withstand the heavy pressure produced by the ventricle during systole.

A valve which was found to satisfy these demands was provided in the following way: a

superficial vein was turned inside out so that its intima was on the surface. Through the adventitia lumen of this valve was passed a tendon—in the human being, the palmaris longus. This gave substance to and increased the size of the valve, and provided a strong resisting structure which wore well, and was found to be in good condition after seven years working within an animal's heart.

This valve is placed to act as a ball valve in the opening made by resection of a portion of the mitral valve. It is passed through the heart and suspended between the anterior and posterior walls with such slackness that during systole it is blown into the defect in the mitral valve. At the same time it is placed far enough down on the ventricular side of the valve, that



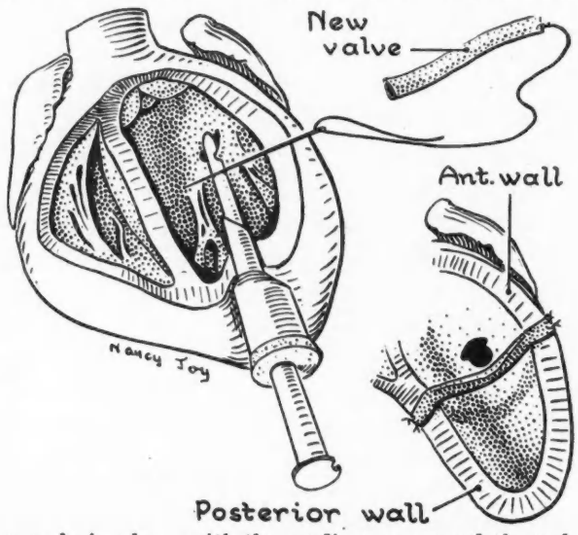


Fig. 2.—Interior of the left ventricle with the cannula in place, with the cardioscope passed through it in the larger diagram, and the punch in the smaller one. **Fig. 3.**—Interior of the left ventricle with the guide hooked on to the valve ring and the needle crossing through its groove in the guide. On the end of the silk is the valve which is drawn through the heart by this suture. The insert shows the valve lying in position in the left ventricle, from which position on ventricular systole, it is blown into the defect in ball valve fashion and floats out freely on diastole.

during diastole it floats out of the opening and lies clear in the ventricle and does not obstruct its filling. When two such structures are placed side by side within the ventricular cavity, they are effective in guarding quite a large opening in the mitral valve. Originally this was done by using surface markings on the heart and thrusting it through from before backwards.

The approach is made through a small incision in the left ventricle through which is passed a cannula guarded by a valve, much as is used in a cystoscope. The punch or knife is passed through the cavity of the ventricle to the mitral valve. The instrument is guided through the opening in the valve by palpation with a finger which has invaginated the left auricle into the funnel shaped orifice. Either a cut is made or a portion is taken out, as desired. Using the left ventricular approach is much easier than that through the auricle, in my experience. There is less hæmorrhage because there is pressure in it only for a short time and the remainder of the time it does not bleed. Secondly, it is thick-walled, does not tear, and is easier to control throughout.

Following this original blind method, a measuring stick was made which was passed through the cannula and by means of a notch on one side, the area of resection of the valve can be felt. At a point five-sixteenths of an inch proximal to this notch, there is a groove in the measuring stick. When a needle is passed through the anterior wall of the heart, the groove in the measuring stick can easily be felt and this directs the valve to the right place. The needle is then thrust through the posterior wall of the heart, the measuring stick removed and the valve drawn through into position.

All this worked very satisfactorily and it was surprising how well experimentally we were able to place these valves, and how well they worked.

It seemed an advantage if we could do this under still better control. For that reason, a cardioscope was devised (Fig. 1). This instrument was made much like a direct vision urethroscope. However, the blood in the cardiac cavity is an opaque medium which prevents vision. Therefore, the instrument was made of a hollow tube with a flat window of glass at the far end. This window is pushed against the surface of the structures to be examined within the heart cavity, so that there is no intervening blood to obscure vision, and

with distal lighting one can see within the cardiac cavity. The valves can be seen, also the hole that is made. The needle as it comes through the heart wall can be seen and under direct vision it can be directed to the right place on the posterior wall. After it has gone through, it can be inspected to see that it is in the right place or whether it should be placed in another position. It can be decided whether the tension is right and whether the valve is stopping the defect in the resected mitral valve as desired.

Using these methods,[21] with or without the cardioscope, we have operated upon ten patients and the results in eight have been fairly satisfactory. Postoperative heparinization was used.[23]

All those operated upon were in the later stages of mitral stenosis. The youngest was 23 and the oldest 47, most being in the forties. All had failure with œdema, and seven had marked ascites requiring paracentesis. All had dyspnœa at rest and six had orthopnœa. There was mild or medium cyanosis in all and all had increased venous pressure with marked distension of external jugulars and enlarged livers. Eight had auricular fibrillation. All had enlarged hearts, some were enormous.

One who did not survive was a patient who was in an extreme stage of failure, had an enormously enlarged heart and was in extremely poor health throughout, with fluid in all serous cavities. While he survived the operation, he did not recover following this. The second failure was one who stood the operation very well, but succumbed on the second postoperative day from pneumothorax, the cause of which was not determined.

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TREATMENT OF THE INFLAMED SKIN*

Lemuel P. Ereaux, M.D., C.M.

Montreal, Que.

THERE is a constant demand on the part of physicians for directives in the management of eczema—dermatitis. There exists "The Fear of Skin"[1] amongst us, for many doctors develop an inferiority complex when confronted with a case of dermatitis.

The following notes deal only with the fundamentals of skin therapy. By them it is hoped to give the uninitiated some added assurance when handling these important problems of cutaneous medicine. At best, this outline will serve only as a first-aid plan for skin therapy, for no all-embracing plan can be laid down for treatment of all dermatological conditions.

The skin is the body's frontier organ. As a surface organ completely unrolled, it is, by its position, vulnerable to attack by outside agents, as well as to endogenous saboteurs who operate from within. Bacterial hordes, parasites, both of animal and vegetable types, await their chance to break its barriers or to lurk within its folds. Household and industrial contactants wear down its bulwarks, while the elements and physical agents, both of the natural and of the atomic variety, may burn away the skin's protective shield. Sensitizers met with in nature, from plant, animal and chemical products, set up fiery irritations on its surface. The chemical compounds, the drugs, dyestuffs, antiseptics, the soaps and the cosmetic aids to feminine beauty account for the greatest damage to man's natural armour. Thus, civilized man, with the development of new plastics, insecticides, soap-substitutes, daily wears down his own outer defences.

Man further paves the way to attack by multiple substances, normally withstood and tolerated, by lowering his threshold of skin toler-

* Read before the Dermatological section, Canadian Medical Association, Saskatoon, June, 1949.

ance. This he does in this enlightened age of self-medication, by saturating himself with the sulfas and the antibiotics in ever-increasing quantities for each and every illness. We are raising a generation of sulfa and penicillin sensitized individuals by such tactics.

Kalz[2] has noted skin polysensitization following the parenteral administration or topical application of these drugs, in persons who previously had handled many household or industrial substances with impunity. He found that after sulfa and penicillin medication, some persons were unable to touch again the products originally used in their trades. Thus, these miracle drugs are opening the flood gates to a tidal wave of new skin allergens. The healing touch of the physician with his skin remedies may even prove to be the hand of a traitor. A sensitized skin may be converted into a battlefield with the irritating application setting up a dermatitis venenata. The greatest single problem in dermatology is the conquest and eradication of dermatitis. Perhaps a review of the possible progression of the stages of a dermatitis might clarify the therapeutic measures, the understanding of which is so necessary to effect relief and cure.

An erythema of the skin resulting from a contact and/or endogenous irritant may progress in one of three ways: From the erythema: (1) To the formation of a papule, and then directly to scale formation. (2) (With stronger irritation) to the papule, and thence on to vesicle formation. (3) (In the presence of a severe irritation), directly from the erythematous stage to the vesicular stage. From the vesicle, three possibilities hold: (1) The vesicle may be absorbed and dry to form crusts, and then progress to scale formation. (2) The vesicle may rupture, discharge, remain open and give rise to a weeping dermatitis. (3) The serous content of the vesicle may become infected, giving rise to the pustule. The above elements represent an acute dermatitis.

With the healing process, weeping and the pustular stages go on through the crusting stage to scale formation, then we are dealing with the subacute stage. A continuing irritative process brings about the response of skin thickening, *i.e.*, drying and fissuring, setting the stage for a chronic dermatitis.

The dermatological classification of the stages of a dermatitic process is not based on the time factor, but rather on the histological progression and on the clinical appearance. This classification is exactly determined on the basis of the type and quantity of the development of the component elements of the dermatitis. Thus:

1. An acute dermatitis is composed of the elements of erythema, papules, vesicles, bullæ or pustules.
2. A subacute dermatitis is one with these primary lesions present to a lesser degree, and the whole process tending towards drying or early crusting scale formation.
3. The chronic stage represents drying, scaling and hypertrophic thickening, with possible fissuring.

It must be remembered that in all of the dermatoses, the three stages may co-exist side by side or occur on the same person's skin in different sites. If a chronic dermatitis breaks down to become moist or infected, it loses its chronic status and reverts to the classification of an acute dermatitis.

Dermatoses are intriguing problems to the scientifically inquisitive minds in medicine. One must have the investigative mind of a detective and the patience of Job to find solutions and cures. An orderly approach aids in finding a solution of the cause of a skin condition and a planned course of therapy accelerates the healing process. "Always look first—question afterwards", and avoid leading questions when interviewing a patient with a dermatitis. Remember to palpate by finger or to use glass pressure in making a direct examination.

In making an examination of the skin, observe the following points in appraising the eruption: Individual lesions. — Their size, shape, colour, raised or depressed, characteristics of border—elevated or depressed, etc. Consistency of lesions —whether dry or moist—their location, arrangement, and distribution—extension or regression.

The eruption.—(1) Evaluate the stage and intensity of the process, with the character of predominant lesion and its position and the presence of secondary changes. (2) Infected or non-infected or local heat? (3) Arrangement of lesions (isolated, grouped, discrete, coalescing, irregular). (4) Note changes due to scratching or to previous treatment. (5) Test sensation (anæsthesia, hyperæsthesia, paræsthesia, pain).

By this time one has gained a clinical impression as to the type of the dermatitis under consideration and has possibly made a diagnostic classification. A diagnosis is considered after: (1) appraising the clinical picture; (2) culling pertinent facts from the history; (3) interpreting special tests.

In attempting to make a diagnosis: (1) think in terms of commonplace conditions. ("Rare dermatoses are 'rare birds', indeed, in dermatology"). (2) If in doubt, do special tests: serology, cultures, biopsy, blood chemistry, patch tests. (These had best be withheld until the acute phase has subsided).

Therapeutic objectives. — When confronted with the problem presented by an acutely inflamed skin, we can do no better than aim at Sir Norman Walker's list of therapeutic objectives: (1) to ease itching; (2) reduce hyperæmia; (3) soak up discharge and cleanse the skin; (4) supply deficient skin fat; (5) in short, to put the skin at rest, so as to allow Nature to perform a cure. Walker stressed that, as long as there is great hyperæmia and discharge, soothing therapeutic measures are safer and more satisfying to the patient than stimulating ones.

H. Radcliffe Crocker, many years ago, stated that "the treatment of eczema (dermatitis) is very important and its mastery will give the key to the treatment of three-fourths of the inflammatory diseases of the skin."

Attempt to remove the surface and/or endogenous irritant (the cause of the dermatitis), and by continuous applications, soothe the inflamed skin. Gratitude from patients to their physicians for release from the itch of dermatitis many times exceeds the thanks given to surgeons for life-saving operations. With an erythematous, hot and swollen skin, one desires to cool the congested overheated surface. Dissipation of the local heat is necessary for comfort. We sometimes forget that ordinary tap water, without added medication, when applied at frequent intervals as an interrupted moist compress, will give greater comfort than expensive complicated preparations. Here the added danger of the irritating action of chemical ingredients is avoided. Much comfort has been afforded to sufferers when cow's milk, either chilled or warmed, has been applied to the inflamed unbroken skin surface of a dermatitis. Here, cooling open compresses (without oiled silk), evaporating lotion, powders or shake lotions, cold cream, thickly applied for its evaporating effect will give comfort. With progression to the papular stage, increased exudation gives rise to swelling with resulting itching. Then one uses compresses, evaporating lotion, shake lotion, powder.

Increased inflammation, accompanied by exudation of serum and the formation of vesicles, requires astringent action to dry smaller vesicles. This is accomplished by applying calamine lotion as a moist compress (kept moist). Evaporating lotions, with alcohol content or compresses, will give an equivalent result. Larger or ruptured vesicles need also to be dried. Paradoxical as it may seem, we dry a serous surface with moisture in the form of hot or cold moist compresses, wrung to the consistency of wet blotting paper. Absorption of exudates can also be effected by starch poultices or ointment dressings.

If the vesicles have become infected, greater moisture, for its softening effect, may be necessary when compresses of the closed type, covered by oiled silk, will soften up the exudate and infected tissue. It is wise not to carry on moist compresses of either type for continuous and prolonged periods because of the danger of macerating the skin. Infection is liable to be spread into surrounding tissues when the skin becomes soggy. In older patients, restrict compresses to but 1/3 body surface and apply wet dressing for short interrupted periods only.

Gauze is to be used in several thicknesses for the application of moist compresses, while surgical lint or old cotton or linen strips will be found more acceptable by the patient for ointments. Gauze has an unhappy faculty of wasting ointment and allowing penetration of the grease into the dressing rather than remaining on the skin surface, and it also tends to adhere to ruptured skin.

"Know your basic remedies and all things in dermatological therapy will be added unto you." Do not rely solely on surface applications by their own action to promote a healing effect. Nature must be aided in getting rid of necrotic tissue and the products of inflammation. It is at this point that one employs one's most valued tools in dermatology—tissue forceps, curved scissors and the scalpel. Debridement carried out with these instruments allows of action of the remedies with resultant acceleration of healing. Remember that surgical cleanliness is next to dermatological salvation.

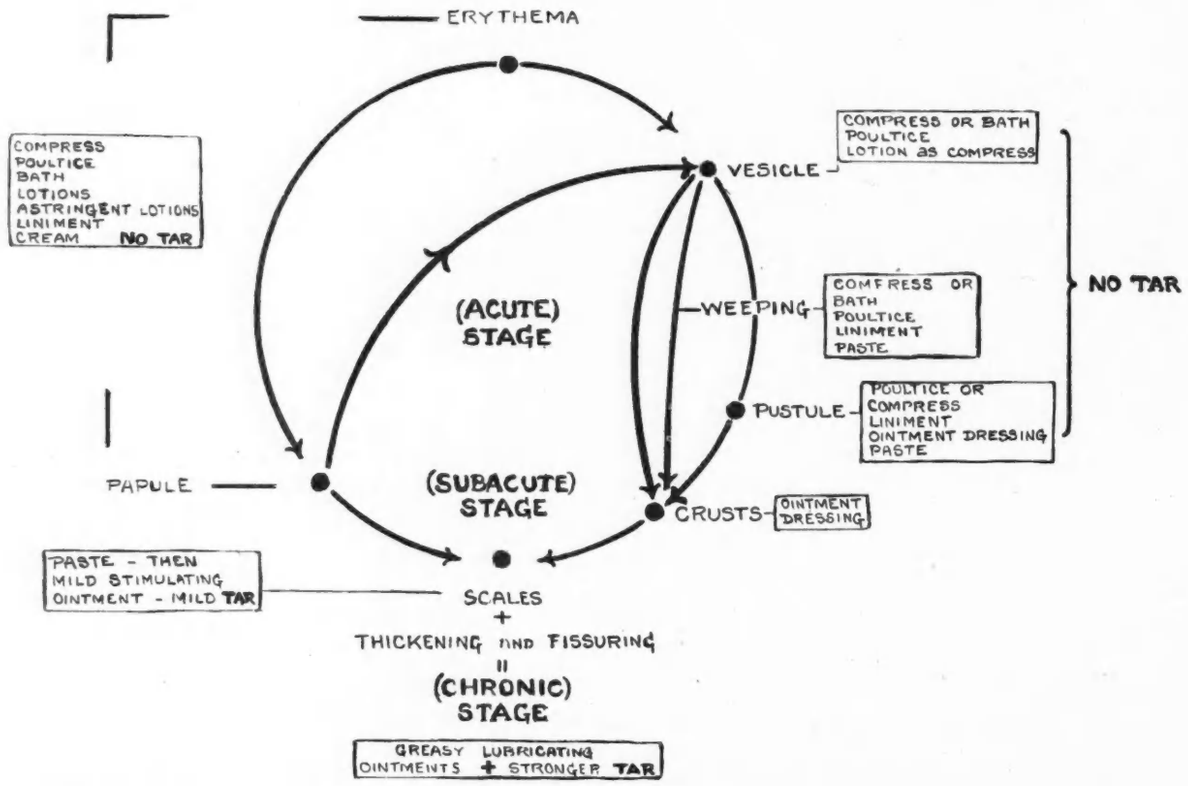
There is a stage of dermatitis which is not usually recorded in the textbooks. I have facetiously labelled it: "The Asinine Stage of Dermatitis". It is the intermediate stage between the ending of the subacute phase and the

starting of the chronic. The skin, like a donkey, during this stage at times will not be budged. One successfully reduces the acute inflammation with bland therapy, dries the secretions with a paste, and then hopes for progression to crust and scale. When mild stimulating therapy is exhibited, instead of progress to healing occurring, the dermatitis breaks down and starts to weep again. It is here that fine judgment, acquired by long experience, plays a part and choice of suitable therapy is all important to effect a cure. Then, like the skin man in the poem, we try again:

"With ointments bland he tries his hand to soothe—but ere too late,
If soothing makes them worse, again, then he can stimulate;
If stimulation aggravates, his course runs ever smooth,
For he can cease to stimulate, and start once more to soothe."

Kindness to the skin was drilled into us by Dr. Philip Burnett. He taught skin appeasement from his wide experience and judgment acquired in the British and Continental schools. We are aggressors with stimulating remedies only when dealing with rebellious chronic resistant dermatoses. Over-treatment methods are responsible for much discomfort to patients and for increased income to dermatologists.

The proprietary cures dispensed over the counter by commercially friendly drug clerks, the home remedies of sympathetic friends, and, alas, the ambitious formulæ prescribed by ourselves and fellow practitioners have, unfortunately, on occasions burnt our patients' skins to a ruddy crisp. Better leave the shotgun proprietary products alone unless their composition and action are clearly understood. These cure-alls, as advertised, should cure everything from falling hair to athlete's foot. Actually, on occasion, they only further aggravate inflammation and fail to give a healing effect. The profession needs to return to first principles in skin therapy, and should avoid trying the shorter route with patented formulæ; the fewer the ingredients of skin remedies, the simpler their composition, the lesser the number of potential skin sensitizers to which the inflamed integument will be exposed.



Dermatitis may prove to be an expensive illness to the patients. Prescriptions should be prescribed in small amounts. These should be used on small areas until their efficacy is determined. Otherwise, patients will remember you with unmixed feelings when they have a bathroom shelf filled with unused jars of ointments which have proved unsuitable for their skin.

Protect parts from friction and order rest if the extremities are involved. A soldier with inflamed feet cannot be sent back to the line of duty; neither can a workman continue at his job with inflamed hands. Any infection of the skin with an accompanying lymphangitis and adenitis is worthy of bed rest, and immediate constitutional care for the accompanying sepsis.

The erythema - papule - vesicle - pustule - scale sequence encountered in dermatitis might well be compared with the rubor, calor, tumor, dolor of the ancient physicians. Dolor, the itch of dermatitis, is a constant early symptom encountered much earlier in skin inflammation than is pain in general pathology. Itch is the one symptom from which patients demand immediate relief in dermatology, and it is the most resistant one to therapy. Itch is encountered to some degree in practically all stages of skin inflammation. There is no one preparation for the permanent relief of intolerable itching. Many applications are suggested, but the temporary superficial relief they afford may be offset by an added dermatitis venenata resulting from sensitization of the skin to the anti-pruritic. By and large, the various "caine" derivatives—novo-, benzo-, supra-, etc.—live up to the reputation of their notorious namesake.

If anti-pruritics are employed, keep their concentration down to ¼ or ½% for avoidance of complications. Remember that menthol applied in a concentration of 1 or 2% to large skin areas gives the patient a chilly sensation which is not easily forgotten.

For internal use, mild sedation with the barbiturates is to be desired above the relaxation obtained from the morphine derivatives. The sting of the morphine group is increased pruritus on the following day, to say nothing of the danger of addiction if their use is continued. Bromides, with their attendant dangers of brominism, had best not be employed. With caution, demerol or codeine may be administered in combination with the aspirin compounds or with the barbiturates for the relief of itching. Do not, however, lazily mask dermatological symptoms with strong sedative remedies.

In atopic dermatitis the barbiturates are worthless to produce sleep. Small doses of barbiturates which may give sleep in the early stages of the condition will have to be steadily increased to near toxic amounts to give the patient rest. Invariably, as the doses are doubled, the aftermath on the skin represents exacerbation and intensification of the dermatitis. The intravenous use of calcium gluconate and calcibromate gives temporary symptomatic relief.

The types of topical applications and their action on the skin might well be briefly reviewed.

Powders are mixtures of solid drugs in finely divided form. Each individual powder particle, like a cube with one face resting on the skin, increases the skin surface for dissipation of heat. Powders absorb secretions and serum by capillary attraction, producing a cooling sensation. They form a protective covering and with suitable additions, give the desired antiseptic, anti-pruritic effects.

Shake lotions, with their ingredients in solution or suspension in the liquid vehicle, are ideal applications for inflamed unbroken skins. When glycerine is added to the lotion, the tendency of too rapid drying is prevented. In action, lotions may be antiseptic, anti-pruritic or astringent. The cooling effect is more pronounced than that obtained by dusting powder, due to the evaporation on the skin surface of the liquid content of the lotion and resulting precipitation of powder. From the practical point of view, they are cheaper to purchase than ointments, go farther on larger surfaces and are easier to apply.

Pastes are a type of thick ointment made from bases of animal fats or vegetable or mineral oils or wetting agents, with an equal amount of powder added. Pastes absorb, lubricate superficially and act as vehicles for topical medications.

Emulsions are oil and lotion combinations. Emulsions stand mid-way between lotions and ointments in their action. They are more easily applied to large areas than ointments, and are better sustained by patients. They can be activated with added antiseptics, anti-pruritics or stimulating additions.

Ointments are the most widely-used preparations in dermatology. They contain a greater percentage of ointment base than that of powder or added medicaments, and they therefore act as lubricants to supply the deficient fat to the dried-out skin. Absorption of grease from the skin surface causes swelling of the horny cells with resultant retardation of evaporation of sweat. Ointments, in a sense, act like a fur coat covering, sealing in the

warmth, if hyperæmia is present. Because of their greasy base, they are rarely suitable applications for oozing surfaces. If used on an infected or a moist surface, they should be applied thickly on lint as a dressing to the skin (an ointment dressing). The type and quality of the base determines the degree of penetration of the contained drug into the horny cells. Ointments are composed of greasy or non-greasy bases, made from animal fats or vegetable and mineral oils. The modern bases, with wetting agents and glycerine content, are more penetrating, more hydroscopic in action and cleaner to apply than standard older types. Ointment bases are the vehicles which carry selected drugs into the skin and, as in most acute dermatitis, the inflammation occurs near the skin surface. We agree with Sulzberger that wetting agents, aiding deeper penetration of drugs, are not always desirable.

The therapy of dermatitis can be carried out with the following basic preparations:

Cleansers—Local.

(*a*) Moist dressings (compresses): warm or cold, of open or closed type. Plain water compress: used warm or cold. Simple boracic acid or saline compresses: 3i to 1 pint of water. Antiseptic compresses: potassium permanganate 1:10,000. Ichthyol boracic: 3i of each to 1 pint of water.

(*b*) Poultices made with corn starch or laundry starch, to be applied cold or warm.

(*c*) Baths (general): After bath, dry the skin by patting skin surface with towel. No rubbing. Alkaline bran bath: Use baking soda with oatmeal or bran. In cheesecloth bag, ½ to 1 lb. cattle feed or oatmeal bran. Infuse like tea bag and use in bath in place of soap. (½ lb. soda [baking soda] to bath.) Starch (corn or laundry), ½ to 1 lb. Prepare with cold water, boiling to clear, as for laundry use. Then stir in warm bath. $KMNO_4$ bath: 5 to 15 grams well dissolved in 30 gallons of water. *Caution*: baths, if too hot, dry the skin and are debilitating to the aged.

(*d*) Powders: starch, talc, etc.

(*e*) Lotions: calamine—liq. plumbi subacetatis Fort., 3 T to 1 pint aq. (astringent).

(*f*) Ointment dressings: lubricate skin after applying a non-greasy cleanser. Boracic acid ointment thickly applied on infected lesions.

(*g*) Oil dressings: mineral oil. Olive oil.

(*h*) Soaps: castille. Non-perfumed, dye-free types.

Pastes.

Pasta simplex, Pasta Lassar's.

Emulsions.

Calamine emulsion (liniment).

Ointments.

Simple: greasy—ung. calamine, ung. zinci oxidi. Antiseptic: ung. ac. boric, ung. diachylon. Stimulating: crude coal tar 3%, starting with milder and then working up to stronger (5 to 10%) concentrations. Use in conjunction with base made of simple or Lassar's paste, calamine or zinc ointment. Bases: standard type (benzoated lard, lanolin, petrolatum, ung. aq. rosea) singly or in combination. Absorptive penetrating (eucerin [aquaphor], hydrosorb, etc., unibase). Newer types.

An accurate diagnosis is a prerequisite for a sound therapeutic approach but all factors contributing to the inflammation are some times not clearly understood at the start. Therefore, it may be necessary to commence symptomatic treatment at once on the basis of the visible disease and at the same time as the investigative procedures are being conducted.

Multiple causative agents may give rise to similar patterns of skin eruptions; sometimes, however, specific clinical entities result and are a great diagnostic aid to the harassed dermatologist. Etiological factors have still to be discovered and eliminated; for cures will not result in the presence of a continuing irritant. Even while investigation is going on, the patient demands comfort and relief of his itch. Granted that the industrial patient has been withdrawn from his previous environment at loss both to his employer and to himself, or that he has covered his exposed skin with protective clothing and has continued his duties, his skin needs care and, if unsuitable applications are applied to his already sensitized skin, increased irritation with resulting prolonged disability may ensue.

More care in the selection of topical remedies is to be desired. The practice of frequent change of formulæ, at the time of repeat visits, has its disadvantages and, if impatience is added to skin care by the patient or doctors, look out for complications. Sound advice and direction still are components in the dermatological formulæ.

Accept gratefully a small therapeutic gain and continue treatment with a well-sustained ointment rather than impatiently changing to a new or unproved preparation. Build new or more active remedies on the foundation of a base which already is known to suit the patient's skin. Sometimes failure of therapy can be traced to simple ingredients, such as boracic acid, paraffin, olive oil, etc., which prove themselves sensitizers, rather than healers in the dressing.

Treatment principles noted in the following chart will be found useful in the therapy of infantile eczema, atopic dermatitis and dermatitis venenata, with its contact variants found in industry and the home. They may be used for any of the dermatoses, clean or infected.

SUMMARY

A TREATMENT PLAN

1. Outline a course of treatment; select remedy to treat predominant lesion.

TABLE I.

TREATMENT OUTLINE OF ECZEMA—DERMATITIS

		Predominant lesions								*Indicated treatment*									
Stage	*State*	*Erythema*	*Papules*	*Vesicles*	*Pustules*	*Crusts*	*Scales*	*Skin thickening*	*Type of skin therapy*	*Compresses - open*	*Compresses - closed*	*Bath*	*Poultice*	*Powder*	*Lotion*	*Cream*	*Liniment*	*Paste*	*Ointment*	*Ointment dressing*
(1) Acute and weeping inflammation	Dry	E	P						Soothing	X		X	X	X	X	X	X			
	Weeping	E	P	V					Soothing and absorptive	X	X	X	X				X	X		
	Infected	E	P	V	Pus.				Soothing absorptive, antiseptic	X Antiseptic	or X	X	X				X	X		X
(2) Mild inflammation	Dry	E	P			C	S		Soothing, mildly stimulating	X		X			X	X	X		X	
	Weeping	E	P	V		C	S		Soothing, astringent, mildly stimulating	X Antiseptic	or X	X	X		X as comp.		X	X		X
	Infected	E	P	V	Pus.	C	S		Soothing, astringent, antispetic	X Antiseptic	or X	X	X				X	X		X
(3) Chronic dry thickened inflammation	Dry	E	P			C	S	S.T.	Lubricating, stimulating or specific	X	X To macerate					X	X	X	X	

2. Give explicit treatment directions to patient or nurse (written directions; avoid confusion).

3. Demonstrate how dressings are to be applied.

4. Remove infected material by moist dressings, etc. Debride the skin detritus, drain vesicles, evacuate pustules.

5. Appraise the action of the chosen specific remedy on your patient's skin by means of a therapeutic patch test on small area for twenty-four hours.

6. Run a comparative treatment on a second site if the eruption is extensive.

7. Treat patient, as well as patient's skin.

8. Avoid rigid faddist dietary restrictions; don't starve your patient.

9. Bed rest at home or hospitalization, if the case is rebellious to cure.

10. Anticipate your patient's demands in difficult cases by suggesting a consultation. By this move, you may win friends and continue to influence your patient.

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1390 Sherbrooke St. W.

THE SURGERY OF PROSTATIC OBSTRUCTION*

James M. Campbell, M.D.

Saskatoon, Sask.

THIS paper deals mainly with transurethral surgery, and is an attempt to analyze the mortality and morbidity in 500 consecutive patients who had prostatic obstruction of an order which required surgery. These cases were operated on during a period of three years. No attempt will be made to disparage or compare the results in any other type of prostatic surgery. It is my purpose to set forth the methods used in this group of cases, and to list the results, both good and poor.

First a word of introduction which may explain the very large percentage of transurethral surgery which was carried out. My predecessor in practice began to operate transurethrally in 1934 and most of the patients were resected from 1934 until 1946. Transurethral surgery was widely known throughout the area of Saskatchewan from which the patients come and, on entering practice, I realized within a few months that, if I did not resect most of these cases, the patients would have the operation done elsewhere.

Now I do not agree that this is in itself a reliable argument that the method of surgery is preferable to other methods. The public may be easily misled and the history of surgery holds numerous examples of operative procedures which enjoyed great enthusiasm for many years only to be abandoned at a later date. The public have little information on which to base proper judgment except casual things such as, there is no cutting in this operation, and, the patient is only in bed for two or three days following the operation. I do not present this enthusiasm on the part of the public as a proper argument in favour of the procedure. The only reliable approach to an evaluation of the various methods of prostatic surgery consists in the careful follow-up of cases by the surgeon and unbiased reports as to his findings. This present series consists of patients who were all in need of early surgical relief of their obstruction. Most of the cases were admitted to hospital in complete retention and many had been catheterized before admission. The remainder were cases of extreme prostatic difficulties with multiple night voidings, thin and dribbling stream and substantial amounts of residual urine.

Of the 500 cases, 62 were reported as carcinoma of the prostate, and 61 were operated on transurethrally. The remaining case had a partial suprapubic removal of the gland because of a long, narrow stricture which contraindicated the transurethral approach. The average age of the carcinoma patients was 68.4 years. There were two postoperative deaths; one was due to pulmonary embolism, and the second to pyelonephritis and uræmia. There were also two late deaths in patients who had metastatic disease and who were relieved of their urinary obstruction satisfactorily, but who, on account of debility and pain, continued in hospital. These died five and three months postoperatively. Three cases have returned for secondary resection. The largest amount of tissue removed in a case of prostatic cancer was 58 grams; the average amount of cancerous tissue removed was 17.8 grams. The results of this treatment, coupled with the other types of surgical and medical therapy, were, on the whole, satisfactory. None required suprapubic drainage and their general well-being was thereby greatly improved.

In addition to this operative series, there were several cases of prostatic carcinoma which did not require surgery; no urinary obstruction being present. There were two cases of marginal obstruction where catheter drainage was instituted for a week or ten days and this, coupled with stilbœsterol therapy, enabled the patient to carry on without too much difficulty.

The only technical point in connection with transurethral resection in carcinoma is one that deals with extreme narrowing of the prostatic urethra due to the growth of the tumour. On three occasions the prostatic urethra was dilated so that the 24 F. sheath could be introduced. Following the removal of 15 to 20 grams of tissue with this instrument, the channel was enlarged to a degree that the 28 F. sheath could be introduced and the remainder of the resection completed. In no case did postoperative hæmorrhage occur.

There was one case of incontinence following resection. This patient had advanced prostatic malignancy where the tumour had invaded the urogenital diaphragm. The patient had been

* Read at the Annual Meeting of the Canadian Urological Association, in Montreal, April, 1949.

operated on elsewhere and, in my enthusiasm to do a thorough resection, he was left incontinent. There were no cases of incontinence in the surgery of benign hypertrophy, and indeed the literature shows that it should almost never occur with operators of experience.

The second group of cases consists of 438 patients who had prostatic obstruction due to benign hypertrophy. The average age in this series was 68 years. They were all cases of advanced obstruction and 12 of them were admitted with cystotomy tubes or suprapubic trocar drainage. The majority of the others required immediate relief by urethral drainage on admission to hospital.

A word about the conditions under which this surgery was carried out. There were no urological interns in the two hospitals in which this work was done—no residents and no assistants. The ward work was done by experienced orderlies whom I have found to be more competent than the average intern not specially interested in urological surgery. The preoperative routine was a little different from what is usually cited in the literature. No surgery was carried out until a complete urological review was done; urethral or suprapubic drainage was continued until the kidney function stabilized. However, surgery was done if the blood urea did not come to normal levels. This is one of the important advantages of transurethral surgery. Preoperative recheck consisted of a cystoscopy in each case. No attempt was made to discharge the patient at too early a date. The distance from which the patients come, the severity of the winter weather and its effect on communications made it advisable to keep every patient under observation for 14 to 16 days following operation.

The benign series of 438 cases is divided for purposes of comparison into the first 238 cases, and a second group which consists of 200 patients. The two series show an increased use of transurethral surgery and a comparison of the results is of some interest. In the first 238 patients, transurethral surgery was done in 88%; the remainder by two stage or single stage suprapubic prostatectomy. In the second series of 200 cases, 96% were operated on transurethrally and the remaining 4% were done by single stage suprapubic prostatectomy. The indications for suprapubic prostatectomy were glands estimated above 100 grams; large glands in healthy men in the younger prostatic age groups, and adenomas in urethras of small calibre where the 28 F. sheath could not be easily introduced. External urethrotomy was not done to enable the resectoscope to be passed.

MORTALITY

I am not too impressed by statistics relating to mortality in prostatic surgery. The reports of small series have no real meaning. As we all know the mortality depends on the stage of the disease, the patient's health and age, and the kidney function.

I include every death that occurred postoperatively in hospital. In addition, there is one patient who died a few weeks after discharge from hospital of urinary sepsis and uræmia. Medical and surgical deaths, due to other than urinary causes, are all included if they were postoperative. In the 438 cases there were 16 deaths. Nine of these occurred in the first 238 cases, giving a percentage of 3.8. Seven deaths occurred in the last series of 200, giving a mortality of 3.5%. A few of the deaths will be briefly reviewed because they indicate the type of case which did not survive.

A man of 78 years developed profuse hæmorrhage from a large prostate. A single stage enucleation was done to control bleeding. The patient died from pulmonary embolism a few hours postoperatively, as demonstrated by autopsy. The second patient, aged 77, had gross bilateral hydronephrosis with urinary retention. Following resection, he was up and about and developed an acute severe gastroenteritis with fever. Pyelonephritis set in and he died of uræmia. Another patient, aged 83 years, was admitted with suprapubic trocar drainage. Following a period of drainage, transurethral resection was carried out. Death was due to pyelonephritis and uræmia. Another patient, aged 69, had a colostomy from a malignancy of the sigmoid. He developed complete urinary retention. Resection was done to relieve the obstruction. He died following this operation of pyelonephritis and uræmia. His blood urea stabilized at a high level but, because there was no other possibility of relief, he was operated on.

There were four deaths in the series due to pulmonary embolism, which were proved at autopsy. One death occurred in a patient who developed a gastric hæmorrhage and later a perforated gastric ulcer, death occurring two days after laparotomy. Another patient was admitted to hospital with suprapubic trocar drainage. He had a very fine stricture requiring internal urethrotomy and gradual dilatation of the urethra. Retention still was present following the dilatation of his stricture. Transurethral resection was done. He returned to his home and a month later developed influenza and pyelonephritis; he died of uræmia. Another patient, aged 74, had a very severe diabetes. He died postoperatively of pyelonephritis and uræmia.

In the series of 438 cases, there were three patients who required suprapubic excision of very large diverticula of the bladder, prior to the prostatic surgery. There were six cases re-

quiring cystotomy because of large stones and 16 cases requiring lithotrity, in addition to resection. One patient, very debilitated, had a transurethral diverticulotomy with removal of a moderate sized stone from the enlarged stoma of the diverticulum. Lithotrity was then done and transurethral resection.

In the resection cases, surgery was confined to one hour. The maximum tissue removed in one hour's dissection was 92 grams. Larger glands, except in very frail or poor risk patients, were done by suprapubic methods. In the first 238 cases, the average weight of tissue removed was 27.6 grams, and in the last 200 cases, the average weight of the prostatic tissue was 31.2 grams.

Postoperative complications. — There were three cases of urinary extravasation. These were treated by immediate cystotomy drainage with a small catheter and drainage of the prevesical space. There were no deaths. It seems to me that if extravasation is diagnosed, and operated on promptly, it is not too serious a complication. Nevertheless, if resection is to be carried diligently to the capsule, it is bound to happen occasionally.

There were three cases of secondary hæmorrhage which required readmission to hospital. In addition, there were 16 cases that required the removal of the catheter during the immediate postoperative period and the introduction of a 24 F. sheath for the removal of clots. Only two of these cases required anæsthetic and there were no deaths. There were no cases requiring cystotomy for hæmorrhage. This conceivably could occur but, according to the writings of experienced resectionists, it is a most unusual requirement.

Epididymitis is not usually a serious complication. It occurred in 11% of the cases. However, most cases responded to the usual treatment and the condition resolved. In four patients, suppuration supervened, requiring incision and drainage. Epididymo-orchidectomy was not done. However, in retrospect I feel it would have been an advantage in two cases.

Most surgeons who have no enthusiasm for transurethral technique speak considerably of stricture as a complication. The evaluation of this complication in my own cases is not at a stage where one could have a definite opinion. Only two of my cases were treated for complicating urethral stricture. What is more important, following a man who did transurethral surgery for 11 years, I have seen only three of his patients who have developed stricture. I do not believe it is very common, if care is taken; if meatotomy is done and the sheath and the urethral canal re-lubricated during the operation; if indwelling catheters are used to increase urethral calibre; and if suprapubic surgery is done where the urethra is definitely of too small a calibre to accommodate the 28 F. sheath. I use the 24 F. sheath at times on small glands and bars. In my hands, however, it is not a satisfactory instrument for the speedy removal of tissue. No sheaths larger than 28 F. are used. There is one other type of stricture that is infrequently mentioned in the literature. I have had one case of my own and have seen one case from the practice of another surgeon. This is the fibrous occlusion of the vesical neck. It is not indeed unknown in suprapubic surgery. The bladder neck heals over except for a small passageway. In the one case I resected, the opening was dilated and the small resectoscope introduced and the fibrous tissue removed. I prefer resection to urethral dilatation for this type of stricture.

The criterion which I accept for a satisfactory result in hospital is as follows; the patient must void a satisfactory stream without distress or symptoms of any kind. Having no residual urine is not the important feature. We all know how a patient can have no residual one day and the next day fail to empty his bladder. The important thing is to remove the adenomatous tissue and have the patient void a good stream.

The next important consideration in morbidity is the progress of the patient and the speed with which his urinary infection clears. All except a very few cases clear of urinary infection within a three month period. There were four cases that had persistent pyuria and recurring episodes of dysuria. These were all advised to return to hospital for further surgery. Two failed to return; the remaining two had secondary resection with satisfactory results.

Here again my own series is not of sufficient duration to allow of definite conclusions. However, I have the benefit of living in an area where there were many cases which were operated on over a period of 11 years, and it is indeed very unusual for me to see one of my

predecessor's cases with recurring symptoms. I know of a few that have drifted elsewhere but, on the whole, the number is insignificant. There seems to be no doubt that as one's ability in this technique grows, the results are increasingly satisfactory. There is really no doubt that patients whose health is poor can be operated on transurethrally and get relief from their condition with a lower mortality than by any other method. Some men resect glands of over 100 grams. However, on general grounds it seems to me that suprapubic enucleation is more desirable than a two- or three-stage transurethral resection.

What then is the place of this method of surgery? The full development of the technique is essential if one is to operate on cancer of the prostate in a satisfactory manner. It is an essential technique in the transurethral removal of benign tumours of the bladder, and low grade papillary carcinoma of the bladder with small, non-infiltrating stocks. In benign enlargement of the prostate, it provides a low mortality and, with proper technique, a good result. With improper technique, the results are poor. This is the reason why there is still surgical argument about this method. If we in Canada are to teach men to do this operation properly, we must see to it that there are facilities for training our men in the fashion of the leading American clinics. Residents should be able to take out 60 grams of tissue in an hour before they are turned out as properly trained men. This can be accomplished if proper teaching methods are followed, with individual instruction under the closest supervision. The student will then finish his training with a degree of technical ability which will enable him to proceed into practice and most of the poor results will disappear.

415 Avenue Bldg.

Dicoumarol was administred to 80 patients with congestive heart failure; a group of 100, similar in types of heart disease, age and severity of heart failure, served as controls. The mortality rate in the dicoumarol-treated group was about one-half that of the control group, apparently due to the prevention of embolic complications. Dicoumarol, under proper control, is considered to be a valuable adjunct in the therapy of congestive heart failure.—Harvey, W. P. and Finch, C. A.: *New England J. Med.*, **242**: 208, 1950.

EMERGENCY OPERATIVE TREATMENT OF FRESH FRACTURES

P. G. Costigan, B.A., M.D.

Atkin Clinic, Banff, Alta.

THE following article will be restricted to the surgical treatment of fresh fractures of the tibia and fibula. During the past three years we have treated over three hundred fractures of these two bones, many of them requiring open reduction before stabilization of the fragments could be achieved. Fractures in all bones have been treated as emergencies and the results have been so gratifying that we feel they will be worth recording here.

The majority of these accidents have occurred while skiing, and are classified as torsion fractures of the tibia and fibula. As a rule both the tibia and fibula have been fractured, either at the same level, or more commonly, the tibia through the lower one-third, and the fibula through the upper one-third.

Occasionally we find that where the skier has fallen forward over the ski-harness, the tibia is fractured through the lower one-third, but the fibula remains intact. This type of fracture as a rule does not present a problem with respect to stabilization of fragments, because the fibula acts as a perfect splint for the tibial fragments, and if the fragments have remained in position throughout the original impact, then they will not be dislodged, or moved out of alignment by the manipulation entailed in the application of a full length plaster cast.

Transverse fractures are the result of greater trauma than the torsion or spiral fractures. As a rule, they occur from being struck by an automobile bumper, or a falling lump of coal, rock or piece of timber. Usually tibia and fibula sustain a transverse fracture at the same level, or when the cause is a glancing blow, the fracture of the fibula will be one to three inches above that of the tibia. These fractures as a rule are compounded, which should place them at the top of the list as far as an emergency stabilization and closing of open wound is concerned.

The comminuted fracture in the lower third of the leg is usually the result of a shattering force; this type of fracture occurs often in ski-jumping, or sometimes while skiing in soft snow the skis will sink below the surface and the crust of snow will strike the lower leg. During the fall, the leg twists in the harness and a com-

minuted fracture of the tibia and fibula is sustained. Usually in this type of injury there is a large butterfly fragment that has been displaced from the anterior surface of the tibia. The superior end of the butterfly has lost its blood supply, the periosteum having been torn from the periosteum of the upper fragment of the tibia. In fractures of this type that we have treated by open reduction, the lower portion of the butterfly fragment has always retained a small blood supply due to the fact that it still retains its periosteal attachment to the lower fragment of the tibia. We are most careful in stabilizing this fragment to make sure that the continuity of the periosteum is not interfered with in this area. Just how much blood supply is retained would be difficult to say, but it gives one the feeling that the complete fragment will not have to revascularize itself.

There is another fracture that we occasionally see that requires operative intervention in order to prevent non-union or fibrous union. This is a fracture of the medial malleolus, where the whole malleolus has been torn away from the shaft of the tibia; or where quite a portion of the malleolus has been torn away from the shaft. Where the piece is small, less than 50% of the malleolus, a fibrous union or non-union will not interfere with the efficacy of the mortise. As a general rule the fragment is displaced anteriorly; and a bit of periosteum or not uncommonly the deltoid ligament is wedged between the fragment and the shaft of the tibia. The radiological examination may not show this position of fragments. We make a practice of taking an x-ray with the patient standing up if possible, with the affected foot flat on the plate and if the leg from the ankle to the knee forced laterally. A picture taken in this manner will almost invariably show a fair separation of fragments, due to the interposition of soft tissue at the posterior margin of fracture line. This type of fracture is operated on immediately, the soft tissue is retracted from between the fragments, and the medial malleolus is screwed to the shaft of the tibia, To assure that the fragment is tight against the shaft, we usually maintain alignment with a towel-clip while the screw is being inserted. The common mechanical complication that occurs here is the rotation of the fragment on the screw postoperatively. We have been guarding against this by the use of a full length plaster cast for a period of six weeks, followed by a walking caliper for from four to six weeks. In using the full length plaster it is not necessary to have the screw pass through the cortices. The drilling of a hole for a screw in this small fragment sometimes is a nerve wracking procedure; and we have found it much easier to drill through the proximal cortex only, and insert a screw at least one inch and a quarter.

Certain types of ski falls will produce a subperiosteal fracture of medial malleolus with no displacement; so at the present time, if the fragment is quite large, we are using a full length plaster cast with no weight-bearing for three weeks; then a caliper is applied for a further three weeks, at which time an x-ray is taken for evidence of union.

Recently some fracture clinics have been recommending open reduction and plating with a special type of plate, dog-eared at either end, of transverse fractures of the fibula occurring at the superior margin of the talus; or through the old epiphyseal plate. They state that unless the fragments are approximated and the plate applied a synostosis will be formed at the level with a non-union of fragments. We have seen only one non-union at this level. This fracture had been treated elsewhere and came to us three months after treatment complaining of pain and swelling over the lateral malleolus; x-ray showed a non-union at the fracture site, with formation of synostosis; the medial malleolus had been pinned to the shaft. This patient was sent back to the operator for assessment.

In dealing with over one hundred fractures in this area so far we have had no non-unions.

TYPES OF INTERNAL FIXATION APPLIED

Some of the most recent articles on types of plates and screws recommended in fracture surgery, have been rather revolutionary in respect to the concepts that we had five years ago. Most fracture clinics seem to be of the opinion that vitallium plates and screws, stainless steel and all recognized materials used in open reductions, do not constitute a foreign body when in place; and any reaction that occurs is probably between the metals themselves and not between metal and bone. Thus it would seem that in treating a fracture by open reduction, a minimum amount of metal should be used to maintain adequate stabilization, and where possible it would be wise to use screws alone, rather than screws and plate. The length of the screw

at one time seemed to be all-important. A post-reduction plate with the screws just through the opposite cortex looks very nice mechanically. We measure the approximate length of the screw by passing a Kirschner wire through the drill hole until it protrudes from the opposite cortex, then inserting a screw of same length. The important thing seems to be that the screw passes through both cortices. Recently a plate has been devised in which screws of a larger diameter are being used and the plate is screwed only to one cortex. The distance that the screw protrudes through the opposite cortex has been of no significance in this series of cases with respect to causing ambulatory pain later on. At present we have two or three ski-jumpers with screws protruding well beyond the cortex, who never complain of pain in the area of protrusion. Naturally it should be recommended that the operator measure the length of the screw with a moderate degree of accuracy.

TREATMENT

Following x-ray these fractures are classified as stable or unstable fractures of the tibia and fibula. If stable and requiring only immobilization, a plaster cast is applied immediately; the length of the cast to depend on the position of the fracture. Simple fractures of the lower end of the fibula not complicated by dislocation of the talus are placed in a walking caliper; *i.e.*, if the extremity is not too badly swollen. If there is a marked swelling then ice compresses are used to reduce the swelling with the application of a fairly tight bandage, but not a compression bandage. At the most recent refresher course held at the University of Alberta, one of the main speakers urged the use of a compression bandage and discouraged the use of the ice compresses. We have used ice compresses on all fractures of the ankle treated during the past year, and find that if applied soon enough after the injury, the period before swelling has been reduced to the point where a cast may be applied, is markedly shortened over the period required when a compression bandage is used. The pain with ice is much less than with compression bandage, and our results have been encouraging with the use of ice in the region of the ankle mortise.

If we are dealing with an unstable fracture, the patient is booked for an emergency operation, regardless of the day or the time of day. Before operating we attempt to decide the type of internal fixation that will be necessary. Usually we find that when the fracture site is visible, an entirely different method of internal fixation will hold the fragments much more solidly. So far we have been unable to obtain the "Egger" plate which allows the fragments to impact themselves with axial pressure. This type of plate makes use of a large screw hole in the plate itself and a sliding mechanism allows the fracture ends to reoppose as absorption takes place.

The patient is then taken to the emergency ward and following sedation a doctor shaves the leg. Patient is then taken to operating room and the assisting doctor, following the administration of a spinal anæsthetic scrubs the affected leg for the same length of time as the surgeon scrubs. Alcohol and ether are both used in the preparation, then the leg is painted with merthiolate or zephiran.

Pneumatic tourniquet is placed high upon the thigh, but is not pumped up to leg point unless bleeding prevents proper visualization of fracture site. At all times the foot is supported by means of sand-bags on either side. Originally we used a sterile stockingette over the foot up to the knee in which a hole was cut and hole edges attached to the skin edges by means of metallic clips. When this stockingette is in position it does not allow skin edges to be stretched every ten or fifteen minutes, one of the most important parts of the operation; hence we have stopped using it. The foot is draped to the ankle with towel and towel clips, and a sterile sheet is pinned one inch below the patella, to allow ready palpation of the patella and anterior spine and easy visual alignment of the great toe with these two points.

Where it is possible, place the incision over soft parts rather than over bone, then tension, as a rule, is not required to close the incision. We always use a curved incision in this area, the incision usually involving 90% of the lower leg to give adequate exposure. The tibialis anticus is freed from its attachment to the lateral margin of tibia and retracted laterally. We attempt to add a minimum amount of trauma to the periosteum. The least amount of the periosteum that is reflected the better; the major portion of the blood supply comes through this medium. The plate may be placed on the outside of the periosteum. If there has been considerable tearing, just reflect sufficient

periosteum to allow visualization of fracture line. You are operating to obtain a complete anatomical reduction. Self-retaining retractors are a curse when used in this area, because tissues tend to retract and shrink, making it extremely difficult to approximate skin edges in closing the incision. We use very small retractors and shift them often, and every fifteen minutes the skin edges are forcibly approximated, or stretched. Wherever possible save all the fragments regardless of the size and put them back in where they belong. Occasionally one has to reduce the fibula and plate by a separate incision. This is necessitated only where the fractured tibia angulates towards the fibula. We always use the single cortex screw close to the joint to prevent entrance of the screw into the joint itself.

Whenever possible use a bone graft from the iliac crest. Lay the bone graft on the side, under the periosteum, and stabilize by using soft tissue to hold it in position. The bone graft will speed up repair especially in dealing with transverse fractures, where, because of the greater amount of trauma there is more bone necrosis. These bone grafts must revascularize themselves by communicating with the surrounding blood supply. In dealing with a spiral fracture that may be held solidly with two or three screws, a counter sink drill is used on the proximal cortex. A drill hole is made through the proximal cortex, then the drill is replaced by a drill of the same size as screw to be used and the drill hole is continued through the opposite cortex. When the screw is inserted and tightened the head which is the same size as the counter sink drill is buried in the proximal cortex and the last turn or two with the screw-driver will have a tendency towards impaction of the fragments. The collision drill set for open reduction has a special drill for the central portion of medulla; and another size for drill for the opposite cortex, thus when screw is tightened the fragments are impacted. We have not been able to obtain one of these sets. The ordinary Yankee drill seems to be as efficient and probably a little easier to use than the surgical bone drills; with the exception that it is very easy to break a drill while using a Yankee carpenter type of set.

When using a plate, we select one of sufficient length to allow two or three screws to be placed, above and below fracture line. Routinely we place the plate on the lateral side of the tibia; and when the tibialis anticus is allowed to fall back into position then the plate is completely covered by soft tissue. Occasionally in severe cases one is able to stabilize a fracture more easily by placing the plate on the medial side of the tibia.

One of these cases developed a thrombophlebitis following operation with embolic phenomena in the right chest and a resulting pneumonia. There was intense pain in the calf of the leg and region of plantar vessels. The skin edges did not heal and a secondary closure was required to close the superior part of the incision. This patient was transferred to another hospital and approximately one month later the central portion of the plate was showing through the incision. A surgeon elected to remove the plate in the presence of skin infection and a probable osteomyelitis followed. This boy had delayed union, but was bearing weight in twelve months. This case was presented before a surgical board eighteen months later; and the board agreed that the surgical treatment had been adequate and sanctioned the emergency procedure.

We have had one similar case to this, in which the man received a compound fracture of the tibia and fibula. Due to circumstances we were unable to perform an emergency surgical procedure. Five days later a plate was applied to the lateral side of the tibia and primary closure attempted by use of bilateral relaxation incisions. The primary closure failed; and on removal of the cast in two weeks' time, the central portion of the plate was in plain view. Antibiotics were used locally and systemically until the open area seemed fairly clean, a full thickness graft was then applied over the open area leaving the plate intact. Approximately 80% of this graft was successful; following eight months of immobilization he is now bearing weight with almost complete skin healing; and the plate and screws are still *in situ*; showing that in all probability the hardware in this case did not constitute a foreign body, and there was no reason to remove it before grafting.

Interrupted absorbable sutures are used in periosteum; we make no attempt to approximate edges of the periosteum since in our series this has been an impossible task; but where possible edges are pulled towards

each other with this type of suture. Thus if the plate is on the lateral side of the tibia it becomes a submuscular plate, and if on the medial side a subcutaneous plate.

The type of suture used in closing the skin, and the method of placing it seem most important. We have used a continuous absorbable suture, wire, silk mattress, and practically every other type. We have found with each of these types of suture that there is a certain amount of sloughing. Recently we have used a silk interrupted suture placed closely together as near to the margin of incision as possible; just through skin edges on either side of the incision. We have found by stretching the skin edges frequently throughout the procedure and reducing the use of continuous retraction that edges are much easier to approximate. If there appears to be more than the usual amount of tugging to approximate edges then one or two relaxation incisions may be used. Relaxation incisions are used in all compound fractures of the tibia and fibula.

Full length plasters, heavily padded, are applied; a greased tube is placed under the lower leg cast; this is pulled out following application of the complete cast; so that a groove is left for cast cutters. This cast is changed in ten to fourteen days, sutures removed, and a full length plaster applied.

With an occasional exception, these patients are out of bed on crutches within twenty-four hours, going to the bath room and sitting up in a chair with leg propped up. We feel that the most important part of the postoperative treatment is quadriceps exercises. One of the physiotherapists from the clinic visits the patient four or five times on the first day after the operation and explains quadriceps exercises fully; telling the patient why they must be performed with real enthusiasm. During the period of hospitalization, which usually consists of twelve to fourteen days, the physio-therapist visits every day and instructs with respect to the quadriceps. It is unforgivable that a doctor treating fractures of the lower extremity should neglect to instruct his patient in this. The usual excuse is that "if the patient had been placed on quadriceps exercises, then the fragments would not remain in proper alignment". This is an extremely poor excuse, because if fragments will not remain in position during quadriceps exercises, then the fracture has not been properly stabilized. We see so many patients coming here for physiotherapy with almost complete quadriceps atrophy, and a perfect anatomical reduction. There is no excuse for this type of neglect.

We instruct patients to return in six weeks' time for x-ray. As a rule radiological evidence of mineralization of fibrous callus does not appear for five to eight weeks from the time of reduction, and many fractured tibias take longer. The earliest mineralization of fibrous callus we have ever seen, confirmed by a radiologist, was in three weeks from date of injury, in a boy sixteen years of age: he was out of his cast and bearing weight in two months.

Any type of pressure will loosen bone screws, and microscopic necrosis will develop; later on macroscopic necrosis results, and screws may loosen before the fracture has healed. Here it is wise to use external fixation up to the groin until there is evidence of mineralization of fibrous callus at least.

The principles to be kept in mind are: adequate reduction; adequate fixation; graft if necessary.

CASE 1

A girl aged 22 sustained a ski fracture of the lower third of the tibia and fibula at three p.m. She arrived at the hospital from the ski hill at six p.m. X-ray showed an unstable fracture of the tibia and fibula. Open reduction and plating were done at seven p.m. In this case a stable reduction and alignment of fragments was most easily obtained by applying plate to the medial side of the tibia and using a transfixion screw to prevent rotation of fragments. Silk sutures were mattressed to close skin. Post-reduction plates showed good alignment of fragments. This patient had her cast removed and was bearing full weight in eleven weeks with only a one-quarter inch quadriceps atrophy, and at present time has no disability either functional or in her earning power.

CASE 2

A boy aged 17 sustained a fracture of the middle third of the tibia with a greenstick fracture of the upper end of the fibula; he was treated as an emergency. A firmer fixation was obtained by applying a plate to the medial side of the tibia, and using a transfixion screw from anterior to posterior. This boy showed a solid union and was bearing weight without cast in nine weeks. It is interesting to note that in this case after one year's time the fibula has resumed proper anatomical alignment.

CASE 3

A girl aged 24 with fractures of the lower tibia and upper end of the fibula, was treated as an emergency. Plate was applied to medial side because more adequate fixation seemed to be obtained by placing it in this position. This was a very difficult fracture to stabilize. We did not worry about length of screws. This patient was out of bed and playing bridge in twenty-four hours. Second cast was removed in nine weeks. She was placed on partial weight-bearing routine and was bearing full weight in eleven weeks. She has never complained of pain due to protrusion of screws through the opposite cortex.

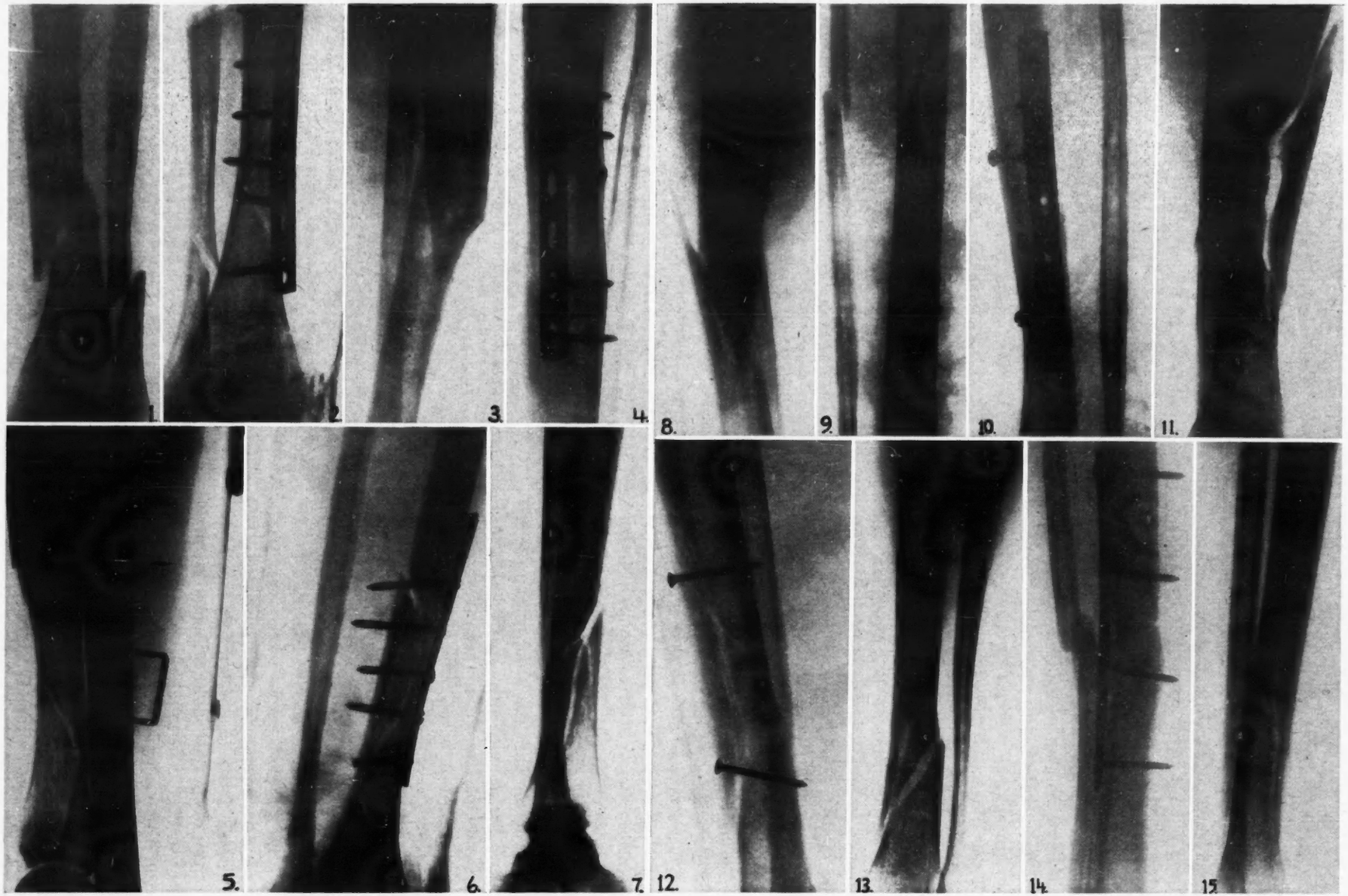

Fig. 1. (Case 1).—Preoperative. **Fig. 2.** (Case 1).—Postoperative. **Fig. 3.** (Case 2).—Preoperative. **Fig. 4.** (Case 2).—Postoperative one year later. Note how greenstick fracture of fibula has straightened out. **Fig. 5.** (Case 3).—Preoperative. **Fig. 6.** (Case 3).—Postoperative. **Fig. 7.** (Case 5).—Original (medial to lateral view). **Fig. 8.** (Case 6).—Original preoperative plate. **Fig. 9.** (Case 6).—Postoperative. This shows proper length of screws. **Fig. 10.** (Case 7).—Postoperative. Showing butterfly fragment screwed into position; and plate applied to lateral side of tibia. **Fig. 11.** (Case 8).—Preoperative. **Fig. 12.** (Case 8).—Postoperative. **Fig. 13.** (Case 9).—Original plate. **Fig. 14.** (Case 9).—Postoperative. **Fig. 15.** (Case 9).—Nine months solid union. She has been out of cast for 3 months with partial weight bearing.

CASE 4

A girl with fracture of the tibia, but fibula has remained intact, thus splinting tibial fragments. She was immobilized in full length plaster cast for six months with no evidence radiologically of mineralization of fibrous callus. Finally in desperation we removed the cast in hope that partial weight bearing and axial pressure would promote mineralization. For approximately three weeks her ankle was quite swollen; then the swelling went down and x-ray one month from the time of cast removal showed bony mineralization. She was bearing full weight in nine months with a solid union.

CASE 5

Comminuted fracture of tibia with fibula intact. This case merely shows splinting action of intact fibula. The fragments were in good alignment with no manipulation.

CASE 6

A girl aged 22, with short spiral fracture of tibia and transverse fracture at upper end of fibula. Treated as emergency fracture, maintained in good alignment by the use of only two screws. The counter sink drill was used here which reduces the fracture line to a minimum on tightening, and has a tendency towards impaction of fragments.

CASE 7

Man aged 27 sustained a comminuted fracture of lower third of tibia, while ski-jumping. Emergency operation revealed a butterfly fracture extending to posterior part of cortex of tibia, and approximately three inches in length. The periosteum between butterfly fragments and lower fragment was intact. The butterfly fragments were screwed to upper and lower fragments of tibia by the use of two A.P. screws. We did not feel that the leg was sufficiently stabilized following this procedure and a plate was applied to the lateral margin of the tibia.

CASE 8

Man aged 27 with typical comminuted fracture of lower third of tibia and fibula. This skier went through crusted snow, the skis stuck and crust struck him in area of fracture. There is a butterfly fragment four inches in length that has retained its attachment to periosteum of lower fragment. This fracture was reduced and solidly held by the use of three screws. Fibula is not in good alignment, but this fact is of no importance as it will heal in this position and give no disability.

CASE 9

Man aged 36, was struck by the bumper of a car and sustained a compound fracture of tibia and fibula. It was impossible to treat this man as an emergency and hence plaster cast was applied and open reduction performed in five days. Primary closure here failed even with bilateral relaxation incisions. Full thickness graft applied over plate. Patient walking in eight months. We felt that his period of time in cast could have been reduced to one-half if he had been treated as an emergency, and primary closure obtained by the use of relaxation incisions, which could have been done had he been treated as such.

SUMMARY

We have recorded our methods of handling over three hundred fractures of the lower extremity in a period of three years. The emergency treatment of these injuries has produced very satisfactory results with respect to almost immediate postoperative comfort of the patient, early ambulatory treatment in physiotherapy clinic, and a minimum number of delayed unions.

Sincerest thanks to Jessy MacDonald, Reg.N., for her assistance in compiling and assembling data required for this article.

Fig. 8. (Case 6).—Original preoperative. This shows proper length of plate.

Fig. 9. (Case 6).—Postoperative. Nine months solid union. She has been out of cast for 3 months with partial weight bearing.

Original (medial to lateral view).

THE SLIPPING RIB SYNDROME

Kenneth M. Telford, M.D., C.M.

Vancouver, B.C.

THE slipping rib syndrome has failed to receive the recognition which it deserves, both in the diagnosis of chest pains by the practitioner and in medical literature. Just thirty years ago the first reference was made by Cyriax.[1] He describes a case in which the patient was relieved of recurrent upper abdominal pain by the removal of the anterior cartilage of the left 8th rib. The cartilage curled up and impinged on the 7th left intercostal nerve. Again Coley[2] described two cases in which the offending displaced rib ends were resected and a prompt cure of this painful condition resulted. Holmes[3] reviewed the literature in 1941 and 1942 and gave detailed histories of 22 cases of this syndrome that he had treated surgically.

This particular syndrome applies only to the cartilage of the anterior ends of the first three false ribs, *i.e.*, the 8th, 9th, and 10th and their interchondral articulations.

CASE REPORT

A 50-year old business executive thought he had had a "heart attack" and was seen about one-half hour later. This shocked-appearing male was lying semi-clothed on the bed with his hand pressed firmly over his precordium. He stated that while dressing, with his left arm abducted, he had experienced an electric shock-like pain which lasted about a minute and was so excruciating that he was almost thrown to the floor. The pain seemed to originate in the left costal margin about two or three inches from the sternum and radiated up his left anterior chest to the shoulder and jaw and down the inner aspect of the left arm and forearm. Physical examination was normal with particular reference to the cardiovascular system. Laboratory examinations including electrocardiograph and a white blood cell count were normal. In the next 24 hours he experienced two lesser episodes of pain again associated with movement of his left arm.

The following day while a more diligent search was being made for the etiology of these attacks the pattern of pain was suddenly reproduced when direct pressure was applied over the 8th rib cartilage. Carefully this manœuvre was repeated three times and each time the patient complained bitterly of pain.

At the time of writing surgery has not been done to relieve this condition but in view of the above-mentioned data a diagnosis of a slipped 8th rib cartilage is established without much question of doubt.

Anatomy.—Each rib consists of a posterior bony part and an anterior cartilaginous portion. The cartilages of the first 7 ribs are attached to the sternum but in the case of the 8th, 9th, and 10th ribs each cartilage is attached to the one above by a dense fibrous mesh which surrounds an interchondral synovial membrane and its joint.[5]

In injury this protective capsule may be torn, allowing the anterior end of a false rib to curl under the cartilage above and impinge on its intercostal nerve or its accompanying sympathetics. By compression of the former nerves, pain will be conducted usually around the thorax to the back.[6] The sympathetic nerves however, with their connections to the cardiac, epigastric and hypogastric plexes, may transmit pain from the thorax to the upper abdomen, and even to the neck, breast, and inner aspect of the arms. It is the transmission of pain to these areas that leads one erroneously to a diagnosis of intra-thoracic or intra-abdominal conditions.

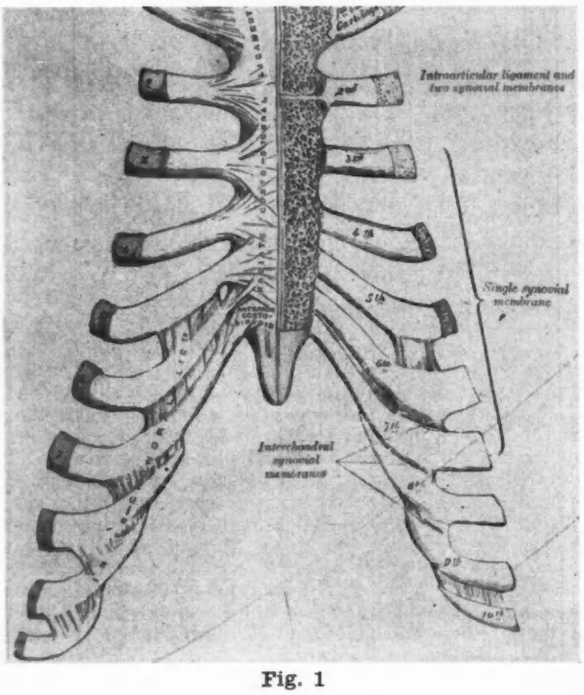

Fig. 1

Etiology.—This syndrome arises from direct or indirect trauma to the chest wall. According to Holmes[4] indirect trauma is the most frequent cause: for example, the various pulls exerted in playing golf, the pulls and pushes of childbirth, one-sided weight carrying as is required in many occupations, and even sneezing and coughing. In 12 of the 68 cases reviewed by Holmes no cause could be found for the displaced cartilage.

Symptomatology.—Pain is the cardinal symptom of a slipped rib. The pain is frequently dull and recurs over a period of years. At other times it is acute and incapacitating and associated with symptoms of shock. Sometimes the pain is precipitated by deep inspiration and expiration as in sneezing, but in others, movement of the body or upper extremities is the cause. Some of the cases reported by Holmes[3] lived in fear of reproducing pain by repetition of one particular physical act. On rare occasions the patient may feel as if "something gave way", or as if there was a "click" just preceding the onset of pain.

Diagnosis.—On examination of the chest wall various degrees of pain may always be produced by digital pressure over the torn or slipped rib cartilage. If the abdominal muscles are relaxed and the pain is not too severe, one hand of the examiner may clutch the costal margin and manipulate it backwards and forwards while pressure is applied over the sternum with the other hand. The oft-repeated click may be felt, and too, in the occasional case, the loosened cartilage may be detected by the examiner's fingers. On occasion the expansion of the chest is limited by the pain. The radiologist can give little assistance in diagnosis except to rule out other disease.[7]

Holmes[3] states, "There must be many cases of obscure chest and upper abdominal conditions that are due to this cause". He urges that rib margins be examined as a matter of routine in cases of obscure chest and upper abdominal conditions, particularly if associated in any way with bodily movements. This obscure pain may have its origin in a slipping rib cartilage. Some laparotomies need not be done, and prolonged suffering may be avoided if this syndrome is sought after and recognized.

Treatment.—The treatment is either medical or surgical depending on the frequency and severity of the attacks. A majority of the cases may be treated by a frank discussion of the condition with the patient and a warning against those physical acts which tend to precipitate these painful episodes. A minority of cases require surgery. At operation, two or three inches of the offending rib cartilage or cartilages are removed. The results after resection are most gratifying.

CONCLUSIONS

1. The "slipping rib" syndrome has received less attention in the medical literature than it deserves.

2. Some cases of obscure chest and upper abdominal conditions are due to this cause.

3. The diagnosis is simple if the examiner keeps the condition in mind. Needless suffer-

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ing may be avoided, and an occasional laparotomy may be prevented.

4. The treatment is either medical or surgical.

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408 Birks Bldg.

RÉSUMÉ

L'auteur passe en revue les différents cas de "slipping rib syndrome" qu'il a relevés dans la littérature médicale et rapporte lui même un cas dans son expérience. Il déplore le fait que l'on n'attache pas assez d'importance à ce syndrome dans le diagnostic différentiel des affections douloureuses thoraciques et abdominales. Le diagnostic en est simple et il pourra parfois éviter une laparotomie inutile. Le traitement est chirurgical et médical. YVES PRÉVOST

A NEW PROTHROMBOPENIC DRUG, PHENYLINDANEDIONE*

L. B. Jaques, M.A., Ph.D., E. Gordon, B.A. and E. Lepp, B.A., R.T.

Saskatoon, Sask.

WHILE dicoumarol has come into widespread clinical use in virtue of its marked ability to reduce the prothrombin content of the blood, anticoagulant therapy with this agent is not ideal because of the slowness of recovery of blood prothrombin levels after administration of the drug has ceased. A definite demand exists for some agent which has the valuable properties of dicoumarol in its effect on prothrombin but which is followed by a more rapid recovery from the effects of the drug.

In 1947 in the course of a study of the relation between structure and anti-vitamin K activity, Meunier, Mentzer and Molho[1] drew attention to the drug phenylindanedione, which showed a transitory effect on prothrombin levels. Soulier and Gueguen[2] later reported on the effect of single doses of this drug. They reported that the drug, in both the experimental animal and in patients, was effective in lowering the prothrombin level, although the doses used (10 to 20 mgm./kg.) were higher than the effective dose of dicoumarol. However, in all cases, the drug caused a more rapid fall in prothrombin, and a more rapid recovery. As this drug does not appear to have been brought to the notice of workers in the U.S.A. and Canada, we[3] have investigated it experimentally and have found that the drug differs from dicoumarol in its action in several important respects, as reported below. An accompanying clinical study of the drug is reported by Dr. A. Blaustein in this number.

* From the Department of Physiology, University of Saskatchewan, Saskatoon, Sask., Canada. Aided by a grant from the National Research Council of Canada. Phenylindanedione (Danilone) was manufactured and supplied by Charles E. Frosst & Co., Montreal.

METHODS

Prothrombin times.—As emphasized by Link,[4] the procedure of Quick is not satisfactory for following the action of dicoumarol. In order to determine small changes in the prothrombin system, it is advisable to modify the method by using diluted plasma. Jaques and Dunlop[5] have shown that after dicoumarol, the prothrombin time becomes very sensitive to changes in calcium concentration, and hence this factor also may be used to make the system a more sensitive indicator of the effects of prothrombopenic agents. In our preliminary studies, we have used therefore a concentration of 0.004 M calcium. In all other cases, we use 0.02 M calcium chloride. Prothrombin times were determined on the plasma itself and also frequently after dilution to 50, 25 and 12.5%. The thromboplastin used was a saline extraction at 53-55° for 15 minutes, of acetone-dried rabbit brain powder. The animals received the ordinary laboratory diet, consisting chiefly of fox chow cubes.

The 2-phenylindanedione-1, 3 was prepared by Dr. A. D. Odell, of the Charles E. Frosst and Co., Montreal, to whom we are greatly indebted. The drug was given orally in gelatin capsules.

RESULTS

Effect of single doses of P.I.D.—To compare the effect on prothrombin time of P.I.D. with dicoumarol, single doses of each drug were given at intervals to a series of dogs and rabbits. Typical curves are shown in Fig. 1. It can be seen that the prothrombin time reached a peak value of 21 to 23 seconds 24 hours after the anticoagulant was administered. However, while after dicoumarol, the prothrombin time took approximately three days to return to normal, after P.I.D., recovery was complete in 14 hours. The prothrombin time after P.I.D., as after dicoumarol (not shown) begins to rise to the peak value after the 10th hour, showing a lag due to the time required for absorption and for its action on the liver(?). However, a definite difference is that P.I.D. shows an effect on the prothrombin time immediately after administration, giving rise to a raised prothrombin time for two to three hours. This effect passes off and is succeeded by the "dicoumarol" effect. This preliminary peak has been observed consistently. As will be reported elsewhere, P.I.D. in comparable con-

centrations does not affect the prothrombin time when added to the blood *in vitro,* so at present we have no explanation for this finding. The prothrombin time values below normal (hypercoagulability) seen in Fig. 1 with dilute plasma were not seen in most experiments and did not occur more frequently than with dicoumarol.

Since the same peak prothrombin time was obtained with 6 mgm. of dicoumarol as with 50 mgm. P.I.D., this suggests that P.I.D. has only about one-tenth the potency of dicoumarol. To test this, the effect of various dose levels of P.I.D. on prothrombin time was studied (Table I).

Examination of this table suggests that there is relatively no difference in the prothrombin time values obtained with different doses of P.I.D. Thus, rabbit 11 showed the same response for doses of 25 and 100 mgm. In contrast, doubling the dose of dicoumarol at these levels, approximately doubles the prothrombin time.[6] With P.I.D. the difference in response between different animals while not marked had a greater effect than differences in dosage level. To our surprise, in several experiments, with doses of 200 mgm./kg. and 20 mgm./kg. in these same animals, no effect was observed on prothrombin time. While blood samples were not taken at sufficiently frequent intervals so that one could say that no change had occurred, in view of the results obtained with intermediate doses, it is surprising that we did not observe some change in the value.

These results are not in agreement with the conclusions of Soulier and Gueguen, who concluded that there was a direct relation between dosage of P.I.D. and the prothrombin time produced. Inspection of the curves reported by Soulier and Gueguen, however, also fails to demonstrate the clear direct proportionality between dosage and effect on prothrombin time observed with dicoumarol.

In view of Jaques and Lepp's demonstration that salicylate has a prothrombopenic action only when given by mouth,[7] P.I.D. was given intravenously to several animals. It was evident that the drug was equally effective by vein and that its action did not depend on the contents of the gastro-intestinal tract as does sodium salicylate. These results indicate that P.I.D. is a weak prothrombopenic agent compared to dicoumarol, but recovery of the prothrombin time is faster following the administration of P.I.D. than of dicoumarol. Meunier[8] has suggested that our failure to confirm the marked effect on prothrombin time with these doses is due to the prothrombin time method used by him being different to the Quick test.

Effect of repeated doses of P.I.D.—In view of the transitory nature of the effect of P.I.D. the effect on prothrombin time of repeated

TABLE I.

EFFECT OF SINGLE DOSES OF P.I.D. ON PROTHROMBIN TIME

Subject	*Dosage mgm./kg.*	*Prothrombin time, secs.*			
		Preliminary peak	*Peak value*	*Time to reach peak pr. t., hrs.*	*Time to return to normal, hrs.*
Rabbit					
11	100	20.0	20.3	18	42
16	100	18.6	24.4	27	45
18	50	18.9	32.7	24	...
19	50	45.6	72.5	27	...
20	50	21.8	29.6	24	30
11	25	....	21.4	24	42
17	25	21.2	28.5	24	42
Dog					
Sa	50	20.5	....	....	33
Sp	50	23.0	30.0	26½	36
P	50	19.2	17.5	26½	36
Rabbit	*dicoumarol*				
16	3	....	38.0	46	105
11	3	....	26.9	24	89
17	3	....	24.8	42	90
18	3	....	32.8	44	92
Dog					
Sa	50	....	43.0	66	92

Prothrombin time with 100% plasma and 0.004 M Ca. normal prothrombin times were 10 to 12 secs. for rabbits, 9 to 13 secs. for dogs.

x—Averages of three and two experiments.

single doses of the drug was studied. Preliminary experiments indicated that it was advisable to administer the drug every eight hours. Various amounts of the drug were given orally to dogs and rabbits every eight hours for periods of from 4 to 46 days. As shown in Fig. 2, repeated administration of P.I.D. resulted in a prolonged prothrombin time. Eight mgm./kg. every 8 hours resulted in a prolonged prothrombin time of over one minute. After 20 days, the drug was withdrawn and it can be seen that in 24 hours, the prothrombin time was normal. This appears to be the most valuable property of the drug. So rapid is the recovery that we have found that failure to ingest a single dose of P.I.D. is reflected in the prothrombin time. This may be responsible for irregularities observed in the figure. Essentially the same results were obtained whether the prothrombin times were determined with 0.004 M calcium or the more concentrated solutions usually used. Due to the insensitivity of the system for slight decreases in prothrombin, the action of P.I.D. is apparently delayed when the prothrombin time is measured with the latter.

Since an amount of drug which had little effect on prothrombin time when given in a single dose, had such a marked effect when the dose was repeated, the effect of number of injections in the twenty-four hours was studied (Fig. 3); 25 mgm./kg./24 hours was given in three divided doses for seven days, then as a single dose each twenty-four hours, and then

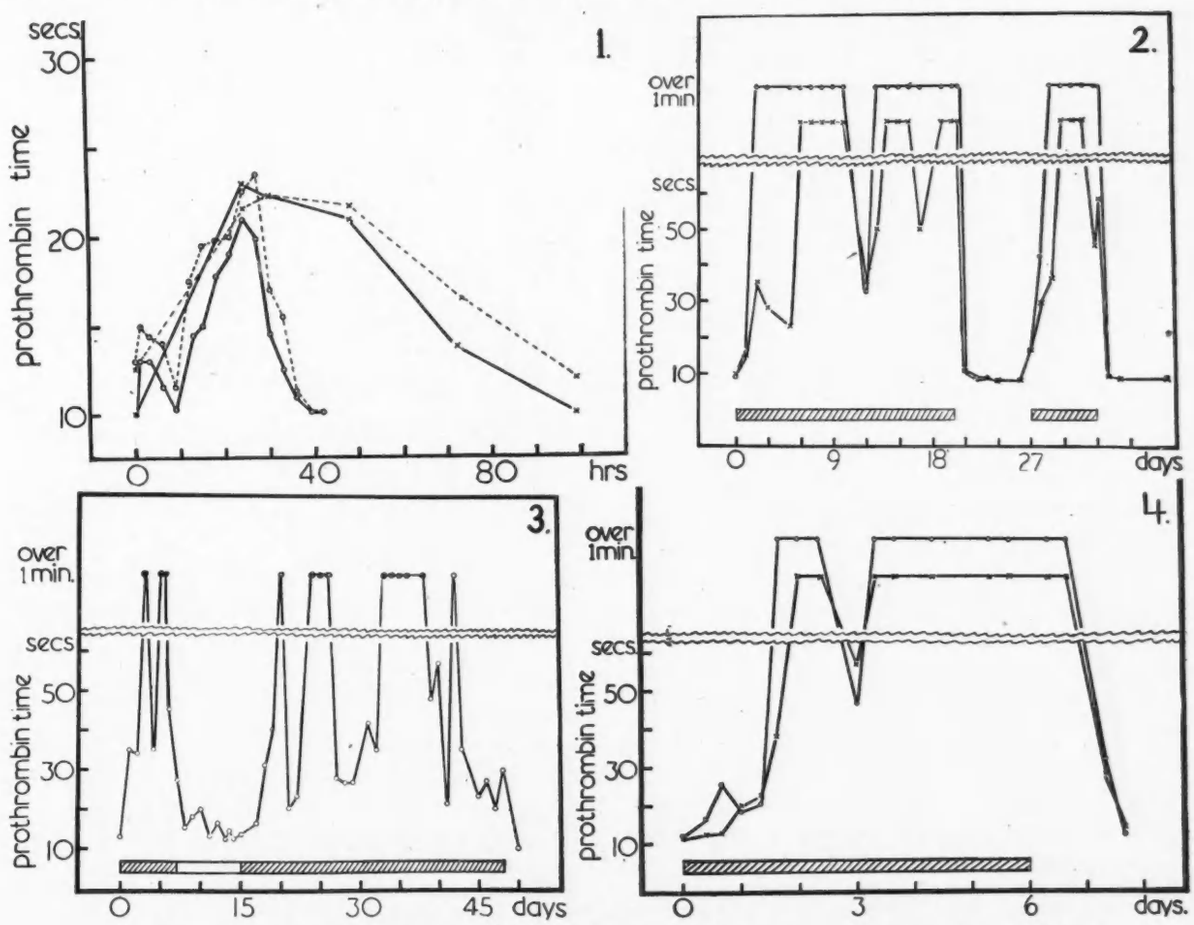

Fig. 1.—Effect of P.I.D. and dicoumarol on prothrombin time in the rabbit. Rabbit No. 11, 2 kg. x———x 6 mgm. dicoumarol 0———0 50 mgm. P.I.D. orally at zero time. Prothrombin time with 0.004 M Ca. Solid line shows values with undiluted plasma, broken line with 25% plasma. **Fig. 2.**—Effect of repeated doses of P.I.D. on prothrombin time of dogs. Dog Sp, 7.1 kg., 8 mgm./kg. given every eight hours. 0———0 prothrombin time with 0.004 M Ca., x———x with 0.02 M Ca. **Fig. 3.**—Comparison of effect of divided doses of P.I.D. on prothrombin time. ——— 25 mgm./kg./24 hours in single dose. ——— 25 mgm./kg./24 hours divided into three equal doses. Dog Pe, 6.8 kg. Ca. concentration, 0.004 M. **Fig. 4.**—Effect of P.I.D. and P.I.D. with vitamin K in rabbits. 50 mgm./kg. of P.I.D. and 50 mgm./kg. of vitamin K per day divided in three doses. x———x rabbit No. 16, P.I.D.; 0———0 rabbit No. 11, P.I.D. plus vitamin K.

finally in three divided doses for a further thirty days. The same rise in the prothrombin time to values above 1′ is observed. Replacing the dose of 8 mgm./kg. every 8 hours, by a dose of 25 mgm./kg. every 24 hours resulted in the prothrombin time falling almost to normal (ranging from 12 to 20 seconds). On the fourteenth day, the blood samples were taken every four hours to determine if there were marked variations in the prothrombin time during one day. Values during the course of the day did not show much variation, indicating that the failure to observe an increased prothrombin time with these single doses every twenty-four hours was not due to rapid changes in the prothrombin time occurring during the course of each twenty-four hour period.

While the dose levels used in Figs. 2 and 3 both give the same extremely prolonged prothrombin time when the drug was administered three times a day, maintenance of very prolonged prothrombin times was not always consistent, since marked fluctuations sometimes occurred in the value and it dropped occasionally for no apparent reason to the range of 20 to 30 seconds (two to three times normal). Several factors appeared to be contributory. One factor was failure on the part of the dog to ingest the drug, in spite of precautions taken to ensure this. Thus, on the morning of the fifth day, the capsule was found in the cage of dog Pe (Fig. 3) and it is suggestive that this failure to ingest the drug on the previous evening coincides with the low prothrombin values on the morning and evening of that day. This same factor may also be operative and explain some of the irregularities during the second period of eight hour dosage. As in this period, the blood samples were taken at much greater intervals, this gave the appearance of much longer periods of decreased prothrombin time and greater fluctuations (*e.g.*, for the twenty-third day). The fact that even missing one capsule per eight hour period affected the prothrombin time response indicates the rapid action of this drug compared to dicoumarol. Another factor operative may have been the protein level of the diet. Meat was fed to animals (Fig. 3) on the 24th to 30th days. It can be seen that the prothrombin time returned almost to normal. Foley and Wright[10] have already suggested that protein intake affects the effectiveness of dicoumarol.

In Fig. 4 is shown the prothrombin time response when P.I.D. was administered to rabbits (50 mgm./kg. was given daily in three divided doses). As with the dogs, a hypoprothrombinæmia was produced. The animals were maintained on the drug for six days. The prothrombin time reached the normal value forty-eight hours after the last dose of drug. The quantitative similarity in the response of the two species is remarkable. Some of the animals studied received simultaneously the same weight of vitamin K (2 methyl 1:4 naphthoquinone) as of P.I.D. and this was repeated at several dose levels of P.I.D. As shown in Fig. 4, there was no difference in response between the animal receiving P.I.D. and the one receiving P.I.D. and vitamin K. Hence, in contrast to results obtained in similar experiments with vitamin K and dicoumarol,[9] giving a weight of vitamin K equal to the weight of this prothrombopenic agent did not affect the change in prothrombin time in any way. Soulier and Gueguen reported that vitamin K had no effect on the increased prothrombin time produced by a single dose of P.I.D.

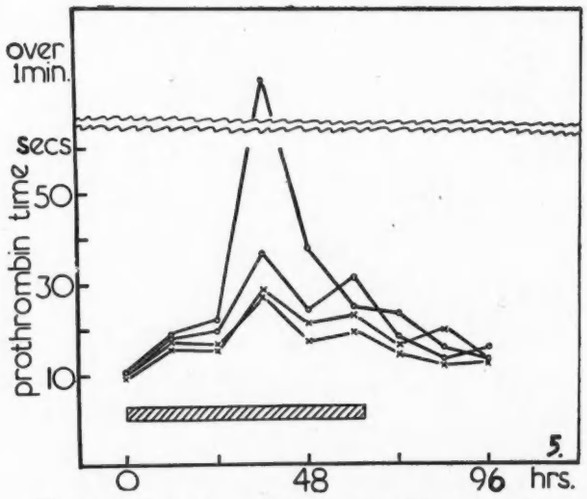

Fig. 5.—Effect of small doses of P.I.D. on prothrombin time. x ———— x 1 mgm./kg. every 8 hours. 0 ———— 0 2 mgm./kg. every 8 hours. Rabbits.

With repeated doses given at short intervals (8 hours), quite small doses of P.I.D. are effective in causing an increase in prothrombin time (Fig. 5). Doses of 2 mgm. and 1 mgm./kg. given every eight hours to rabbits resulted in the prothrombin time being increased to values between 20 and 40 seconds. One sample from one animal gave a prothrombin time of 165 seconds but this was not maintained. Variation during the maintenance period suggested that

some fluctuation in the prothrombin time occurred between dosage periods. With these low dosages, the same rapid rise in prothrombin time at the beginning of the experiment and the same rapid return to normal on stopping the drug was observed as with the high dosages. The effect of varying dosage has not been studied further, as it was considered of greater significance to determine the consistency of the response for the dosage levels selected. Repeated experiments with dogs and rabbits using the 8.3 and 16.7 mgm./kg. doses (25 and 50 mgm./kg./day) consistently gave the response shown in Figs. 2, 3 and 4. Since these dose levels give prothrombin times of infinity they represent the upper limit of dosage. Presumably there is a lower limit of dosage below which the drug fails to affect the prothrombin time. The values shown in Fig. 5 indicate that this level is approximately 1 mgm./kg. It appears that the prothrombin time response does not increase gradually with dosage but rather above an effective dose the response increases very rapidly. The results reported in Fig. 5 suggest that the administration of 3 mgm./kg./24 hours in divided doses maintains the prothrombin time satisfactorily at two or three times the normal value.

Toxicity of P.I.D.—All animals receiving the drug were studied for symptoms of toxicity. As with dicoumarol and any other drug which has a marked pharmacological action, one must distinguish the effects of overdosage of the drug (in this case the effects of a marked decrease in prothrombin) from side effects unrelated to the desired action of the drug and which constitute its true toxicity. A prothrombin time of infinity presumably indicates an undesirable degree of hypocoagulability of the blood and therefore represents overdosage. Hæmorrhage was a definite phenomenon with our animals when the prothrombin time became infinity. Hæmostasis could be satisfactorily produced by ordinary pressure if a 25 gauge needle was used for the blood sample. However, with an 18-gauge needle, hæmostasis was very difficult and prolonged bleeding from the veins tended to occur. There was no effect observed on the red cell, white cell or platelet count after continuous administration of P.I.D. No change was observed in the hæmatocrit value and differential white cell count, which were determined at intervals on some of the animals receiving the drug. Soulier and Gueguen reported renal damage with very large doses of the drug. Therefore, on all occasions when urine was collected, it was examined microscopically, with almost uniformly negative results. Two animals maintained on the drug for a long period of time with very prolonged prothrombin times showed interesting hæmorrhagic episodes. These were precipitated by extraneous factors (not related to P.I.D.) but were very severe. Stopping administration of the drug resulted in rapid and complete recovery. It was our impression, based on previous experience, that these animals would not have survived a similar condition following dicoumarol, without repeated transfusions and large doses of vitamin K.

Several dogs were maintained for fifty days on the drug, with infinite prothrombin times for most of the period, yet showed no hæmorrhagic condition at any time. Two rabbits and one of the dogs studied died during the investigation and a similar number were sacrificed. We are indebted to Dr. D. F. Moore for studying these animals for pathological lesions. No pathological lesions ascribable to the P.I.D. were observed histologically in heart, lungs, liver or intestine. In the kidney, a mild fatty degeneration particularly noticeable in the limbs of Henle's loops, was observed. These animals had received from 0.5 to 3.0 gm./kg. of P.I.D. over a period of some months. Possible long term toxicity of P.I.D. is still under investigation.

DISCUSSION

It is evident from the results reported that P.I.D. possesses valuable properties compared to dicoumarol in its ability to lengthen the prothrombin time, since cessation of the drug results in a prompt return of the prothrombin time to normal levels in approximately twenty-four to thirty hours in the animals studied. A single dose of P.I.D. has only a slight effect but if repeated doses at frequent intervals are administered, the prothrombin time can be increased to very high values. Hence, while with single doses, this drug appears to be a weak prothrombopenic agent compared to dicoumarol, on repeated administration it appears to be as effective as the latter. 3 mgm./kg./24 hours is suggested as a possible routine dose which compares closely with the clinical dose

of 300 mgm./24 hours for dicoumarol. While as with dicoumarol, overdosage with the drug results in a hæmorrhagic condition, cessation of the drug with the resultant return of the prothrombin time to normal completely reverses this serious condition, and hence there appears to be a much greater safety factor with this substance.

It is evident from our findings that the main toxic effects of P.I.D. as for dicoumarol, are associated with its effect on the clotting system of the blood and the resulting effects on the mechanisms of hæmostasis. These effects result when such large quantities of the drug are given that the prothrombin time is increased to infinity. Since clinically the drug will be controlled by determinations of the prothrombin time, such extreme overdosage will be avoided. The drug appears to be excreted by the kidneys, and hence, it is not surprising that it can cause renal damage, probably because of concentration and resulting precipitation of the drug in the tubules. However, Soulier and Gueguen and ourselves have observed indications of such renal damage only with extremely large overdosages of the drug in terms of its ability to maintain a prolonged prothrombin time.

In conclusion, the results of this study demonstrate that while P.I.D. is a poor prothrombopenic agent as judged by the ordinary test used for dicoumarol, it proves to be highly effective when the method of administration is changed. This suggests that the large series of compounds related to dicoumarol already tested for prothrombopenic action should be subjected to re-evaluation.

SUMMARY

1. The effect of 2-phenylindanedione-1, 3 (P.I.D.) on the prothrombin time of dogs and rabbits has been investigated. A decreased concentration of calcium was used in the estimation of prothrombin time to make it a more sensitive indicator of the action of prothrombopenic agents. The finding of Meunier, Mentzer, and Molho[1] that the prothrombin time returns to normal values more rapidly with this substance than after the administration of dicoumarol, has been confirmed.

2. While single doses of this compound had only a slight effect on prothrombin time, it was found that administration of P.I.D. at frequent intervals resulted in the drug being as active as dicoumarol in prolonging the prothrombin time. 8.3 mgm./kg. every 8 hours resulted in the modified prothrombin time becoming infinity after three days. 1 mgm./kg. every 8 hours increased the prothrombin time to approximately twice the normal value. Vitamin K had no effect on the prolonged prothrombin time produced. With withdrawal of the drug, the prothrombin time returned to normal within 36 hours.

3. Following large doses of the drug over a long period of time, a hæmorrhagic condition similar to that resulting from dicoumarol overdosage was observed when other precipitating factors were present. This was rapidly reversed after withdrawal of the drug. No gross toxic effects were observed with 8.3 mgm./kg., administered every eight hours for forty-eight days in dogs.

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A NEW PROTHROMBOPENIC AGENT*

Ancel Blaustein, M.D.

New York, N.Y.

ANTICOAGULANT therapy until recently has focussed attention on heparin and dicoumarol. These agents have been subjected to extensive experimental and clinical studies and their properties and actions are well established. Heparin has to be administered intravenously. It very rapidly prolongs the clotting time but its effect is of relatively short duration and consequently frequent administration is necessary.

The clotting time rather than the prothrombin time is utilized to follow the anticoagulant effect. Heparin appears to exert an anti-

* From the Department of Pathology, University of Vermont, College of Medicine, Burlington, Vt.

thrombin effect and to a much lesser degree an antiprothrombin effect. Protamine sulphate or toluidin blue will rapidly nullify the action of heparin. The advantages of heparin are its rapid action, and the ability to counteract it by the use of other agents in the event of bleeding. The disadvantages are its expense, the need for intravenous route and frequent administration. In an effort to obviate this latter defect, attempts are being made to combine heparin with a slowly absorbed base.

The advent of dicoumarol constituted an important advance in the field of anticoagulant therapy. It is administered in tablet form by mouth and its action is substantially more prolonged than heparin. A therapeutically valuable prothrombopenic level is usually established in from 48 to 72 hours. The initial dosage to obtain this effect is usually divided over a 48 to 72 hour period, *i.e.*, 300 mgm., the first day, 200 mgm., the second day and 100 mgm. the third day. There are other variations of this dosage schedule. Dicoumarol acts in the liver to prevent prothrombin formation. The effect of the drug can be diminished by vitamin K. However, it is well known that if a dicoumarolized patient bleeds the above therapy does not always suffice and whole blood often has to be administered. Many side reactions have been reported, such as skin rashes, diarrhœa, and others too numerous to mention. In summary, the advantages of dicoumarol are the ease of administration, the low cost and a more prolonged anticoagulant effect. The disadvantages are its less rapid catabolism, the numerous side effects and the time required to develop the therapeutic prothrombopenia. Accordingly continued search goes on for more advantageous anticoagulants.

In recent months, I have had the opportunity to utilize a new anticoagulant substance clinically. This substance, phenylindandione, is closely related to dicoumarol in structure. Soulier and Gueguen[1] were the first to use it clinically. In this country Jaques[2] thoroughly investigated the substance and in this issue he discusses its properties and its background. It is given by mouth and is in tablet form. My report is merely a brief preliminary survey on the use of this substance. It is based on its application to 20 patients, 16 of whom had thrombotic episodes in the form of coronary heart disease and thrombophlebitis of the lower limbs. Our studies attempted to answer the following questions. Can the drug be safely administered? What are the initial and maintenance dosage requirements, toxicity if any and effect on liver function?

Dosage.—By the trial and error method we arrived at an initial dose of 150 mgm. to be given as follows; 100 mgm. in the morning and 100 mgm. at bedtime. With this dose we found the prothrombin concentration was altered from its initial value to 25 or 30% in from 23 to 28 hours. Initial doses of less than 150 mgm. took from 30 to 40 hours before any effect was noted. For those who prefer to lower the prothrombin levels to 15% of concentration a dosage schedule of 50 mgm. in the morning, 50 mgm. at noon and 100 mgm. at bedtime appears to obtain this result. One of our cases required 500 mgm. before we obtained the required prothrombopenia. This type of response is similar to what is occasionally seen with the use of dicoumarol. Maintenance requirements depend upon the daily prothrombin time. In our small initial series of cases 51.4 mgm. per day represented the maintenance dose required to keep the prothrombin concentration between 25 and 30%.

Toxicity.—Jaques *et al.*[2] studied the toxicity of this drug thoroughly. They only reported bleeding in dogs that were overdosed with large amounts of the drug. Soulier and Gueguen reported polydipsia, polyuria and rapid pulse as side reactions. We were not able to detect these changes. Three of our patients were clinically overdosed by phenylindandione as evidenced by prothrombin times of infinity. Only one of these patients bled. He had hæmaturia on one occasion which ceased when the drug was discontinued. After administration of the drug is stopped the prothrombin returns to normal in from 48 to 72 hours. Blood sugars, cholesterols, total proteins, serum albumin and globulin, hippuric acid formation and bromsulphalein excretion tests formed the battery of liver function tests performed before and after administration of the drug. There was no evidence of any interference with liver function. The sedimentation rate and white blood cell counts were not appreciably altered by treatment.

Our preliminary studies are based on a handful of cases but they serve to prove several important points. The drug can be given safely. It appears to act in half the time required by

dicoumarol and its catabolism is more rapid. Its actions would place it somewhere in between heparin and dicoumarol though its properties are more closely allied to dicoumarol.

It is my belief that this anticoagulant is deserving of clinical trials in a larger number of cases.

The author wishes to express his appreciation to Chas. Frosst & Co., Montreal, Canada, for supplying phenylindanedione (danilone).

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341 - 353 W. 50th St.

THE PATHOGENESIS OF SECONDARY ANÆMIAS*

G. Malcolm Brown, M.D., D.Phil.(Oxon.), M.R.C.P.(Lond.), F.R.C.P.[C.], F.A.C.P.

Department of Medicine, Queen's University, Kingston, Ont.

THE term "secondary" anæmia is loosely used but it is a convenient name for that large group of anæmias which occur in association with some other disease. It has been commonly believed that these anæmias are dyshæmopoietic in nature and that the disturbance of erythropoiesis is merely part of a general toxæmia or disturbance of metabolism. The anæmias which complicate those infections due to organisms which produce hæmolysins have been the only widely accepted exception to that general proposition. It is the purpose of this communication to put forward evidence that excessive hæmolysis and sometimes abnormal hæmolysis may frequently play a part in the pathogenesis of the anæmia which complicates carcinoma, the reticuloses and also sepsis due to organisms which do not produce hæmolysins in large amounts.

METHOD

Hæmolysis has been studied in these cases by determining the rate of destruction of transfused erythrocytes. The patients are transfused with whole blood or with erythrocyte suspensions belonging to a group other than their own, and the rate at which the transfused erythrocytes disappear from the peripheral circulation has been determined by the method of selective agglutination of the circulating erythrocytes by appropriate high titre sera (Ashby,[1] Mollison and Young[10]). By this method the average life of the transfused erythrocytes in a normal person has been shown to be about 60 days (Callendar, Powell and Witts[3]). This means, of course, that the life span of the erythrocyte is about 120 days, and this value corresponds well with the estimations provided by those who have fed man glycine containing N^{15} (Shemin and Rittenberg[13]) and by those who have used pigment excretion studies as the basis for estimation (Hawkins and Whipple[8]).

In a normal person, when the number of surviving erythrocytes is plotted against time the decay curve is linear and reaches the base at about 120 days. In some cases of anæmia two types of abnormal results may be seen. Firstly, the decay curve may remain linear but have an increased slope reaching the base in less than 120 days. Secondly, the plotted results may show considerable curvature as well as reaching the base in less than the normal time. This latter is the case, for example, in frank hæmolytic anæmias such as Lederer's anæmia. When the decay curve is of this type, the results may be interpreted as providing evidence of the operation of a method of hæmolysis not active in health as well as an increase in the rate of hæmolysis. The hæmolytic process which produces a linear decay curve has been called the *linear hæmolytic mechanism* and that which produces curvature in the decay curve has been called the *exponential hæmolytic mechanism* (Brown, Hayward, Powell and Witts[2]).

An attempt has been made to describe the results of this type of experiment numerically (Brown, Hayward, Powell and Witts[2]), working on the hypothesis that two processes of cell destruction can be distinguished. The simplest algebraic equation which reasonably fits the data in these cases is:*

$$\frac{N}{No} = (1\text{-}Lst)\,\frac{R\exp(\text{-}Let) + 1}{R + 1}$$

which becomes

$$N = No\,(1\text{-}Lst)$$

when the decay curve is linear. From these the average life (t) of the transfused erythrocytes can be calculated, and as well the fraction of the transfused erythrocytes (Fe) which has been destroyed by the *exponential hæmolytic mechanism* and a fictitious average life (ts) of the transfused erythrocytes which would obtain if the *linear hæmolytic mechanism* had been acting alone. The results of the present experiments will be described in this manner.

There are two points concerning the method to be mentioned. One concerns its accuracy. Every one is aware of the degree of accuracy in counting erythrocytes. The accuracy in counting inagglutinable erythrocytes is of the same degree and it has been found that the standard error of the difference between dupli-

* Read at Annual Meeting, Royal College Physicians and Surgeons of Canada, Toronto, November, 1949.

* Notation—

N	=	Donor cell count in recipient at time t, million per c.mm.
No	=	Donor cell count in recipient immediately after transfusion, million per c.mm.
t	=	Time measured from transfusion (days).
Ls	=	Constants.
Le	=	
R	=	
	=	Average life of transfused cells measured from t=0 (days).
ts	=	Average life corresponding to linear component (days).

cate observations is of the order of 6% of the inagglutinable count (Brown, Hayward, Powell and Witts[2]). In the present series of experiments, four counts were made on each specimen and each count was plotted rather than just the average count for the day. Counts were made every other day in the initial period and subsequently at about fortnightly intervals.

The second point concerns the delicacy of the method. It has been found that the method provides evidence of increased hæmolysis and/or abnormal hæmolysis in cases where there is no reticulocytosis, no abnormal bilirubinæmia and no increase in excretion of urobilinogen and herein lies the merit of the method. Fæcal urobilinogen was determined by the method of Schwartz *et al.*[12] (Table I).

TABLE I.

SURVIVAL OF TRANSFUSED ERYTHROCYTES COMPARED WITH RETICULOCYTE COUNT, PLASMA BILIRUBIN, AND FÆCAL UROBILINOGEN

Case	*Reticulocytes %*	*Plasma bilirubin mgm. %*	*Fæcal urobilinogen mgm./day*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
XI	1.1	0.4	12.0	53.0	53.0	0
VIII	1.1	0.4	60.0	40.2	52.5	0.29
XXV	1.0	0.9	130.0	30.0	30.0	0
XVI	1.0	0.5	196.0	21.0	25.0	0.24
XIV	0.8	0.3	20.0	16.8	32.5	0.38
VII	0.6	0.5	0.3*	8.0	8.0	0

*0.3 units in 2-hour urine specimen.

THE ANÆMIA OF INFECTION

The anæmia associated with infections due to organisms other than those which produce hæmolysins in large amounts is usually normocytic and normochromic, but on occasion it may be slightly microcytic and hypochromic. There is as a rule no accompanying reticulocytosis and this with the absence of an increase in the plasma bilirubin and the absence of an increase in the excretion of urobilinogen has led many to the conclusion that it is a dyshæmopoietic anæmia. Vaughan and Saifi[16] concluded on these grounds that there was no evidence of hæmoglobin breakdown in excessive amounts but because of an increased excretion of coproporphyrin I and III they did suggest that there was disturbance of hæmoglobin synthesis. Robscheit-Robbins and Whipple[11] had suggested the same thing some three years earlier. It was a conclusion that was concurred in by such standard authors as Whitby and Britton.[17] Cartwright[4] and his colleagues brought forward in 1946 the hypothesis that the anæmia is due to a disturbance of iron metabolism. They had found that in the anæmia of infection there is a low concentration of iron in the serum, that the iron absorption curve is low, and that iron given intravenously quickly disappears from the blood stream. They suggested that the anæmia of infection is due to a disturbance of hæmopoiesis, the result of a failure to form heme because of the lack of iron to incorporate into the protoporphyrin molecule. Hemmeler[9] in the same year also concluded that this anæmia was due to disturbed erythropoiesis.

In my own experience the examination of sections of bone marrow of the ribs of six patients with empyema has led to the finding of a hyperplastic marrow with a proportionate

TABLE II.

SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF ANÆMIA OF INFECTION

Case	*Diagnosis*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
I.	Septic arthritis	50.0	50.0	0
II.	Pneumococcal empyema	60.0	60.0	0
III.	Pneumococcal empyema	41.5	41.5	0
IV.	Pneumococcal pneumonia	46.0	46.0	0
V.	P. vulgaris abscesses	23.0	23.0	0

increase in the erythroid series. The bone marrow is at least active, even if not efficient.

Study of a group of these cases by the method of transfusion which has been described has led to evidence which suggests that as well as a disturbance of erythropoiesis there is in some cases excessive blood destruction. Table II shows the rate of destruction of transfused erythrocytes in this series, in all but one of which the streptococcus could be excluded. In Case V, a diabetic with multiple *Proteus vulgaris* abscesses, the rate of destruction of the transfused cells was more than twice that of normal. It should perhaps be noted that in this group there was evidence of activity of the *linear hæmolytic mechanism* alone. Similar evidence of excessive blood destruction has been found in an earlier group of cases of infection (Brown, Hayward, Powell and Witts).

THE ANÆMIA OF MALIGNANT DISEASE

The rôle of excessive hæmolysis in the anæmia of malignant disease has been studied in those cases where the issue was not complicated by blood loss, and where the neoplasm did not involve the gastro-intestinal tract. Three of the series were cases of carcinomatosis with widespread secondaries, including involvement of bone. In these cases it is commonly held that the anæmias belong to the myelophthisic group and that it is due to a disturbance of erythropoiesis. A case of bronchogenic carcinoma and a case of carcinoma of the parotid gland completed the group.

TABLE III.
SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF CARCINOMA WITH ANÆMIA

Case	*Diagnosis*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
X.	CA of lung	39.0	48.0	0.22
XIII.	CA of parotid	33.0	33.0	0
XI.	Carcinomatosis (prostate)	53.0	53.0	0
XII.	Carcinomatosis (breast)	33.0	33.0	0
XIV.	Carcinomatosis (uterus)	16.8	32.5	0.38

All five patients destroyed the transfused erythrocytes at more than the normal rate (Table III). In the patient with carcinoma of the lung and in one of the patients with carcinomatosis there was evidence of activity of the *exponential hæmolytic mechanism* as well as activity of the *linear mechanism*. Stats *et al.*[15] have also remarked on the presence of hæmolytic anæmia in a single case of colloid carcinoma probably arising from the colon.

THE ANÆMIA OF THE RETICULOSES

Collins and Rose[5] recently reviewed the problem of the anæmia of leukæmia and came to the conclusion that disturbed erythropoiesis is an essential feature of the disease. Some earlier workers (Jaffé and Kress) had concluded, on the basis of the hæmosiderosis which they found, that excessive blood destruction was the principal factor in the pathogenesis of the anæmia and even suggested that excessive hæmolysis might play a part in the pathogenesis of the leukæmic process. However, Whipple and Robscheit-Robbins found only a little more iron in leukæmic livers than in normal human liver, and Forkner suggested that the hæmosiderosis reported by Jaffé and Kress in acute leukæmia might have been due to the hæmorrhagic tendency their cases showed. The occasional occurrence of hæmolytic anæmia in the course of the reticuloses has been remarked on by Singer and Damshek[14] and by Stats *et al.*[15] The present work suggests that excessive hæmolysis may be present more often than is commonly believed.

TABLE IV.
SURVIVAL OF TRANSFUSED ERYTHROCYTES IN CASES OF THE RETICULOSES

Case	*Diagnosis*	*Average life t days*	*Average life corresponding to linear mechanism ts days*	*Fraction destroyed by exponential mechanism Fe*
VI.	Acute lymphatic leukæmia	23.3	23.3	0
VIII.	Chronic lymphatic leukæmia	40.5	52.5	0.29
IX.	Chronic lymphatic leukæmia	18.0	24.0	0.34
VII.	Chronic myelogenous leukæmia	8.0	8.0	0
XVI.	Hodgkin's disease	21.9	25.0	0.24
XVII.	Hodgkin's disease (a)	63.0	63.0	0
	(b)	40.5	40.5	0
XV.	Plasma cell myeloma.	28.0	28.0	0

In the four cases of leukæmia which have been studied by means of transfusion, there has been evidence of increased blood destruction (Table IV). In three of these cases the increase was marked and in two there was evidence of activity of the *exponential* as well as the *linear hæmolytic mechanism*. Two cases of Hodgkin's disease have been studied. In one of them, the average life of the transfused erythrocytes was greatly reduced, and the decay curve was curved. In the other, the cells of the first transfusion survived for the normal time, whereas a year later the cells of the second were destroyed by the *linear hæmolytic mechanism* at an increased rate. A patient with a plasma cell myeloma also showed excessive activity of the *linear mechanism*.

COMMENT

The results of this experimental method suggest that in three groups of cases, a hæmolytic factor plays a part in the pathogenesis of the accompanying anæmia. This is a view which is contrary to the commonly accepted views concerning the pathogenesis of these anæmias and the results gained by the method perhaps need validation. First of all it can be said that in those cases where there is other evidence of excessive blood destruction, transfused erythrocytes are destroyed more rapidly than normal except in familial hæmolytic anæmia (Dacie and Mollison[7]) and in nocturnal hæmoglobinuria (Dacie and Firth[6]). Secondly, it can be pointed out that there is no evidence from the work with the MNO and Rh groups that cells of Group O are destroyed more rapidly than the patient's own cells when he belongs to another group, and as already mentioned, the figures arrived at for the average life of the erythrocyte correspond well with the estimates provided by means not involving the use of cells of another group. Finally, the conclusions put forward here were arrived at after comparison of results obtained in normal subjects with the results obtained by the same method in the patients involved.

The results show the importance of hæmolysis in the three anæmias considered, and in some of the cases the excessive hæmolysis demonstrated was sufficient to account for the anæmia found. It is to be emphasized that the cases in this series were studied as they became available and were not chosen because a hæmolytic anæmia was suspected on the usual grounds. If study of a larger series provides the same results as the study of this group of 17 cases, it will be apparent that excessive hæmolysis plays a more frequent part in the pathogenesis of these anæmias than is at present recognized. In the majority of cases there was no evidence that there was at work any hæmolytic mechanism other than that seen in the normal subject, even though in these cases there was evidence of increased activity of that process. In the other cases there was evidence of a hæmolytic process not seen in health. This process which has been called the *exponential hæmolytic mechanism*, has not so far been seen except where the *linear mechanism* shows increased activity. The physiological basis of these two mechanisms remains a matter for speculation.

Unfortunately neither the results of this work nor the results of previous work provide any better suggestion for therapy than transfusion. Provision in excess of the known factors required for erythropoiesis has no beneficial effect, and all that remains is to do what can be done about the primary condition and to transfuse when the amount of circulating hæmoglobin is reduced to the point of embarrassment.

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AN OSCILLATORY BED SUPPORT IN PRINCIPLE AND IN CLINICAL USE

E. L. Harrington, Ph.D., F.R.S.C.

Professor of Physics,
University of Saskatchewan, Saskatoon, Sask.

THE general principle of inducing or aiding the circulation of the blood or of other body fluids by the utilization of the effect of gravitational forces on these fluids, though known for centuries, gained wide recognition and became generally employed only during the last world war. Among the several peace-time applications of the same general principles which have been developed recently, may be mentioned an oscillatory hospital bed support which grew out of work in the field of medical physics in the University of Saskatchewan. While the original design provided means of tipping the bed proper about a transverse axis, the use of the longitudinal axis makes possible a very great simplification of the design; in fact, it becomes feasible to use the standard, unmodified hospital bed with all its mechanical features, as well as any attachments employed in special cases. Experience has indicated that a change in blood is the essential need, and that the magnitude of the change in pressure is of minor importance.

The development herein reported has to do with a bed support so designed that the bed is given a slow angular oscillation about a horizontal longitudinal axis without lateral translation. Tests with a number of different observers led to the rather surprising conclusion that a rotation of about 12° from the horizontal plane is sufficient to give to the person on the bed the feeling that he is lying on his side; the explanation being that the plane of the mattress, in addition to the patient himself, is being rotated. It may help to consider the familiar rocking chair; a slight rotation of the chair leads to a relatively large translation of its point of contact with the floor. The smallness of the required amplitude makes it unnecessary to provide the bed with side railings, except in very special cases, since the normal patient feels no danger of rolling off the bed, and it greatly simplifies the mechanical problem of producing the required oscillations.

Briefly stated, the bed, to be rotated, is mounted on two curved steel rails carrying at their ends fixed pins which extend upward into the legs of the bed. Each of these rails rests on a pair of rollers, supported from a main frame, near the floor and as far apart as the amplitude of excursion of the bed permits them to be. Since the centre of curvature of the rail is substantially on the axis of the patient, he is moved neither vertically nor horizontally during the oscillations of the bed; hence the force required for the movement is very small indeed. The supporting framework for the head and the foot of the bed are rigidly joined by a steel pipe through which extends a shaft carrying at either end a crank joined by a connecting rod to its corresponding curved rail. A sturdy, motor-driven reducing gear mounted on the main frame, carries a short crank on its

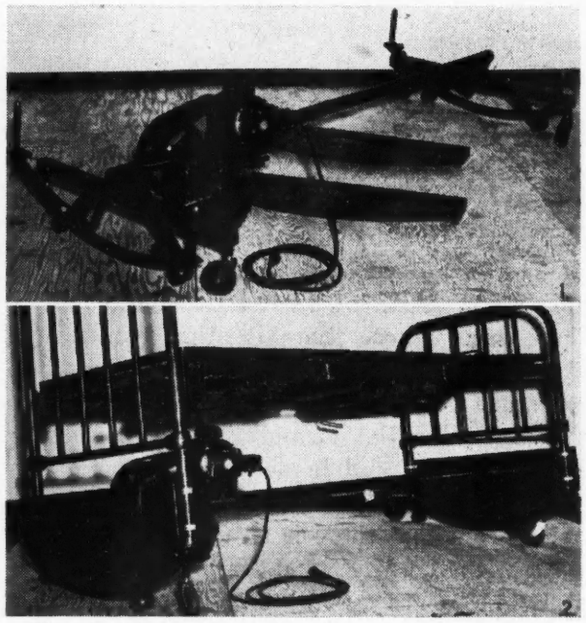

Fig. 1.—Mechanism of oscillatory bed support, including the two end shields, unattached. **Fig. 2.**—Standard (Simmons) hospital bed mounted on the oscillatory support with the end shields attached.

slow motion shaft and thereby gives to the main shaft and to the connected bed rails a correspondingly slow oscillatory motion. As actually constructed, the period required for one cycle of operation is about four minutes, but this is not a critical matter. For the comfort of the patient the period should be long, but not long enough for the blood to become stagnant in any tissue. The motion is so slow that the casual observer may fail to notice either the mechanism or the motion.

Only a brief discussion of the physical and the physiological principles involved is needed to point out the more important advantages of an oscillatory bed support. The entire gravita-

tional force on a person standing erect is exerted through the soles of his feet, which, during his growth, acquire a thickness and a toughness adequate to take care of the rather large forces without injury. Gravitational forces remain vertical whatever the position or angle of rotation of the body. For example, when a person lies on his back these forces act on the blood, on every organ, in fact on every part of the body in a direction at right angles to their directions in an erect body with respect to their corresponding body parts. Any rotational changes lead to corresponding tension changes in the tissues of every part of the body, and movements of every body fluid. In short, they bring about exercise, especially vascular exercise. Unfortunately the weight of the body in the recumbent position is borne by comparatively small areas which, unlike the soles of the feet, are unprepared to match the new demands. In some of these, the pressure due to gravitational forces may be greater than that produced by the heart, hence no circulation can take place in such areas until there is a change in posture. After a comparatively short period, a slight irritation or pain due to the lack of circulation develops and the normal person, though unconscious of it, changes his posture and gives relief to the areas concerned.

But for a patient with, say, a broken femur or pelvis, or one who has had a spinal operation, who may be compelled to remain in a cast for weeks or even months, there is little or no relief ordinarily available. Even with the best of care, bed sores may develop. The period of hospitalization needed is considerably lengthened by the poor circulation and the depression characteristic of such patients. It was for the comfort of these that the bed support was originally designed. It appeared obvious that a rotation of the bed would bring about a shift in the pressure areas, and permit refreshing circulation, thus affording relief in every area and part of the body periodically. It was intended for use also by patients immediately after major operations, to promote the movement of blood and lymph in the regions in which normal circulation is interrupted or blocked. It was hoped that the usual postoperational congestion would be avoided to a large degree, the danger of postoperational pneumonia reduced, and that reasonable comfort would be afforded the patient who normally has to choose between the discomfort arising through his inability to turn, and the pain caused by those who turn him. It was obvious that the rotational movements would favour both digestive processes and excretion. All these objectives are apparently being realized clinically.

The following are extracts from, or abbreviated statements based on clinical reports on cases in which the patients made use of the oscillating bed support herein described.

1. A 70-year old woman suffered from diabetic peripheral disease for three months, which developed into impending gangrene. The foot was cyanosed from the ankle downward and two small gangrenous areas were seen. Along with "other conservative measures" she was treated on the oscillating bed for a period of three months. Within two weeks all pain disappeared, the colour returned to normal, and the dorsalis pedis was palpable. She was able to return home without amputation. (This same experience was repeated in a similar case later.)

2. In the case of Mr. M. who had a fractured thigh, the broken skin on the back healed completely after the patient had been on the bed for five weeks.

3. The oscillating bed was used on Mrs. F. from November 10 to February 15 with extremely gratifying results. "She had a badly fractured pelvis and fractured 1st lumbar vertebræ. Due, I would say, almost entirely to the use of the bed, Mrs. F., whose age was 69 and whose condition was not good at the start, did not have any of the expected complications in which her condition invariably results". There were no respiratory or renal symptoms, no difficulty in keeping the skin on her back and buttocks intact, and she was extremely comfortable throughout. Had the bed not been available, the nursing care of the patient would have been very difficult and there is the distinct possibility that she would not have survived her accident.

4. A man 75-years of age had carcinoma of the prostate with a metastatic lesion involving the 12th thoracic vertebra and producing paraplegia. At the time he was placed on the bed, he had large decubitus ulcers, particularly over the area of the sacrum. Subsequently the ulcers healed progressively and his general condition improved.

5. A man with advanced liver malignancy with metastatic lesions in his spine, was suffering also from well marked decubitus ulcers. This patient stated that he was much more comfortable on the bed; he complained less of back pains and his ulcers healed progressively.

6. On admission, Mr. J.McC. had a cardiac condition complicated by uræmia. He was partially paralyzed. His general condition and that of his skin was poor. Despite the usual precautionary measures employed, the skin on his right buttock broke down and the open area progressed steadily until it was a sloughing ulcer about 2½ inches in diameter and quite deep. It responded poorly to treatment. His condition made treatment difficult, as he was a big man and resented being moved to have his back rubbed. After a month he was placed on the oscillating bed. His general care was facilitated since his bed could be stopped at any angle, and it was easier to turn the patient. The bed sore showed improvement in a few days and healed quickly, filling in from underneath with the improved condition until it was completely healed. The patient's general condition, of course, was also greatly improved.

7. A man 82-years old had a palliative colostomy for an inoperable carcinoma of the large bowel. He was placed on the rocking bed soon after operation and, in addition, he was out of bed for short periods of time on the third day. At no time was he confused as is usual with such elderly cases, and he remained bright mentally.

Striking success has been attained also with a poliomyelitis case with lung involvement.*

On the basis of fundamental principles of physics and of physiology and of clinical observations to date, important conclusions may be supported. Certainly the operation of the oscillating hospital bed enhances the circulation, virtually exercises the whole body of the patient and leads to a better mental outlook and feeling of well-being on his part. The comparative freedom from restlessness is due, no doubt, largely to the better removal of waste products from the various tissues and organs.

Patients in casts, with major fractures or spinal or chest operations, are especially benefited since their posture may be shifted at will without in any way disturbing the position of their body with respect to the bed or to any attached traction devices. Since the bed is of regulation type, all of its regular or its special equipment functions normally and no new techniques need be learned by the attendants. Similar benefits accrue even to patients not in casts following major operations during the period in which the ordinary manipulations by attendants are so painful. Indeed, the degree of congestion normally responsible for much of the pain, may not even develop. The gentle "massage" and hence better circulation resulting from the oscillations of the bed, lead to more rapid healing and make possible earlier safe ambulation and shorten the required periods of hospitalization without involving the hazards inherent ordinarily in early ambulation.

The oscillating bed, whatever the type, seems to offer a definite solution of the problem of decubitus ulcers. They will certainly not form ordinarily or, if already formed, when the patient is placed on such a bed, will progressively heal thereafter whatever the general condition of the patient, assuming the ulcers are not due to causes other than the pressure effect. Every case clinically observed to date supports these conclusions.

* See also an extended report on "Modification of the Effects of Immobilization upon Metabolic and Physiologic Functions of Normal Men by the Use of an Oscillating bed" by G. Donald Whedon, John E. Deitrick and Ephraim Shorr, *Am. J. Med.*, **6**: 684, 1949.

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AEROSOL THERAPY FOR LUNG ABSCESS*

H. E. Christie, M.D., C.M.,†
M. Aronovitch, B.Sc., M.D., C.M., F.R.C.P.[C.], F.C.C.P.‡ and
J. F. Meakins, M.A., M.D., C.M., F.R.C.P.[C.], F.C.C.P.‡

Montreal, Que.

THE treatment of acute non-tuberculous lung abscess has become once more almost entirely a medical problem. Prior to the use of sulfonamides, penicillin and streptomycin, the treatment of this condition frequently required early major thoracic surgery, and was not without a significant mortality. Recent literature cites numerous case reports of successful medical treatment of lung abscess with the aid of aerosol therapy.[4, 6, 7, 8] Very few cases are now referred to surgery.

During the year 1947-48, the authors had the opportunity of evaluating aerosol therapy in eight consecutive patients with acute non-tuberculous lung abscess. We feel our experience is worth reporting.

Material.—The above eight cases were admitted, investigated, and treated on the medical wards of the Royal Victoria Hospital. They are summarized in Table I. There were seven males and one female. The ages varied from 26 to 57 years. The predominating symptoms were cough, sputum, prostration, and dyspnœa. Five were severely ill while three had moderate constitutional symptoms. The onset, by clinical and radiological examination, was considered to follow a pneumonia in seven cases, and an upper respiratory infection in one. One case was complicated by diabetes mellitus. The predominat-

* From the Chest Clinic, Department of Medicine, Royal Victoria Hospital, Montreal.

† G. Rutherford Caverhill Fellow in Medicine, Royal Victoria Hospital, Montreal.

‡ Assistant Physicians, Royal Victoria Hospital, Montreal.

ing bacterial flora in the sputum was *Staph. pyogenes* in three cases, pneumococci in one, and mixed flora in four. The location of the abscess was as follows: right upper lobe, two cases; right lower lobe, two cases; left upper lobe, one case; and left lower lobe, three cases.

Treatment and results. — All cases received intramuscular penicillin. Daily dosage averaged 45,000 units every three hours, eight times a day. Total quantities given varied from 1,920,000 units in eight days to 17,000,000 units in 37 days in the diabetic patient.

All cases received aerosol penicillin. This was administered in 1 c.c. doses five times a day. Each c.c. contained on the average 40,000 units of penicillin. Total quantities given varied from 1,000,000 units in 10 days to 9,000,000 units in 45 days. The average duration of aerosol therapy was 25 days. In one case the penicillin was dissolved in a normal saline solution. In the others it was dissolved in a normal saline solution of epinephrine 1% and ephedrine 1% or neosynephrine 1% in the proportions of 1:9 (see Table I).

Postural drainage was generally carried out before each aerosol treatment. Expectorants, frequent moving of the patient, encouragement to cough and expectorate, breathing exercises with the rebreathing bag containing 95% oxygen and 5% carbon dioxide, were routine. Oxygen was given when indicated.

The results were excellent in all cases. Radiological resolution occurred on the average in 5 or 6 weeks. The total duration of the illness, including convalescence, averaged 15 weeks.

Two case reports are given in detail below:

CASE 2

H.H., male, aged 57. Two weeks prior to admission this patient suffered from a brief upper respiratory infection. One week prior to admission there was an acute onset of fever, chills and dyspnœa. On admission the patient had clinical and radiological evidence of a massive pneumonia in the right lung. He received i.m. penicillin 60,000 units q3hx8 for 12 days, and sulfadiazine orally, 0.5 gm. q4hx6 for 9 days. Temperature and pulse subsided to normal by the sixth hospital day. He continued to do well with clinical and radiological improvement. He was allowed up on the 23rd hospital day. That evening he became weak, acutely short of breath, with a constricting sensation in chest, and a small amount of blood-tinged sputum. The temperature rose to 103°, pulse 130, and the white blood count which had been 7,200 rose to 14,000. An x-ray of the chest revealed a new consolidation in the left hilar area (see Fig. 1a). He was given sulfadiazine and sulfamerazine, *aa* 0.5 gm., q4hx6, for the next 7 days without effect. On the 30th hospital day the patient began to expectorate huge quantities of thick chunky green blood-streaked foul-smelling sputum, about 300 c.c. per day. This sputum grew *Staph. pyogenes* on culture. Five days later there was radiological evidence of an evacuation in the L.L.L. (see Fig. 1b).

TABLE I.

Age and sex	*Symptoms and site of abscess*	*Predominating organisms*	*Treatment*				*Recovery in days*					*Length of illness*
								Cough and sputum		*X-ray*		
			Sulfa days	*I.M. penicillin daily dose*	*Aerosol penicillin daily dose*	*Solvent*	*Acute toxæmia*	*Marked improvement*	*Minimal or none*	*First improvement*	*Healed*	
26 M.	Severe L.L.L.	Mixed flora	35	480,000 18 days	125,000 30 days	Saline	22	10	45	18	38	47 hosp. dys. total 21 wks.
57 M.	Severe L.L.L.	*Staph. pyogenes*, *Strep. Viridans*, Proteus Intermedius.	18	360,000 9 days	200,000 45 days	Epinephrine, ephedrine	18	31	77	35	75	107 hosp. dys. total 20 wks.
55 M.	Severe R.L.L.	Mixed flora and Alkaligenes Fæcalis.	17	360,000 13 days	100,000 20 days	Epinephrine, ephedrine	25	43	52	17	71	52 hosp. dys. total 17 wks.
55 F.	Severe and diabetic R.U.L.	*Staph. pyogenes*	..	480,000 37 days	300,000 37 days	Epinephrine, neosynephrine	11	14	50	12	40	50 hosp. dys. total 12 wks.
39 M.	Severe R.L.L.	*Pneumococci*, *H. influenza.*	..	160,000 12 days	100,000 10 days	Epinephrine, neosynephrine	23	23	35	29	37	37 hosp. dys. total 12 wks.
42 M.	Moderate L.L.L.	Mixed flora.	..	360,000 29 days	200,000 30 days	Epinephrine, neosynephrine	7	10	23	6	36	40 hosp. dys. total 11 wks.
27 M.	Moderate L.L.L.	*Staph. pyogenes.*	..	240,000 10 days	160,000 11 days	Epinephrine, ephedrine	4	4	7	7	15	19 hosp. dys. total 12 wks.
55 M.	Moderate R.U.L.	No pathogens. Isolated.	..	240,000 8 days	500,000 13 days	Epinephrine, ephedrine	11	3	18	16	37	28 hosp. dys. total 7 wks.

Immediately following the onset of the profuse expectoration, therapy consisted of: i.m. penicillin 45,000 units q3hx8 for 9 days, and aerosol penicillin 40,000 units q3hx5 for 44 days. The aerosol solution contained a normal saline mixture of epinephrine 1% and ephedrine 1% in proportion of 1:9, in which 40,000 units of penicillin per c.c. were dissolved. Postural drainage was performed before each aerosol administration. An expectorant of mistura ammonii chloridi drachms iv, was given four times daily to help thin the thick sputum. Breathing exercises with the rebreathing bag containing 95% oxygen and 5% carbon dioxide, were given three times daily. By the 40th hospital day the temperature was normal, cough was much less and the sputum had reduced to less than half (100 to 150 c.c. daily). By the 58th hospital day there was marked radiological and clinical improvement. His cough was slight and he

raised 30 to 40 c.c. of thin whitish mucoid sputum daily. By the 97th hospital day (74 days following his complication) there was no radiological evidence of abscess and the pulmonary infiltrations had cleared markedly (see Fig. 1c). Bronchographic and bronchoscopic examinations pre- and post-discharge from hospital, showed no evidence of bronchogenic carcinoma. The patient has remained well.

The acute episode on the 23rd hospital day may have been a pulmonary infarction with subsequent gangrene, or a frank suppurative bronchopneumonia. It was felt that aerosol therapy with penicillin and bronchodilator solutions, was of considerable value in combating the infection and aiding drainage and expectoration in this case.

CASE 4

M.S., female, aged 55. One week prior to admission this patient complained of severe cough, expectoration of about 60 to 70 c.c. of thick green-yellow sputum, fever, and malaise. These symptoms followed an upper respiratory infection. On examination she was suffering from prostration, mental confusion, dyspnœa, signs of consolidation with râles over the R.U.L., and acidosis from an unsuspected diabetic state. The x-ray revealed a consolidation of the R.U.L. with a cavity (see Fig. 2a). On admission sputum cultures grew *Staph. pyogenes.* Repeated examinations were negative for tubercle bacilli. Treatment of the lung abscess consisted of postural drainage, encouragement to cough and expectorate, intramuscular penicillin, 480,000 units per day for 37 days, and aerosol therapy. The aerosol solution contained epinephrine 1% and neosynephrine 1% in proportions of 1:9, in which 60,000 units of penicillin per c.c. were dissolved. One c.c. of this was given five times a day for 37 days. By the end of two weeks' treatment there was marked improvement in the toxæmia, cough and expectoration. The x-ray revealed the pneumonia to be resolving and the abscess smaller (see Fig. 2b). All signs and symptoms of the lung abscess clinically and radiologically had disappeared by the end of six weeks (see Fig. 2c). Bronchoscopic and bronchographic examinations pre- and post-discharge revealed no evidence of carcinoma. Following a further period of six weeks' convalescence the patient has remained well.

It was felt aerosol therapy with the bronchodilator vasoconstrictor drugs, and penicillin, aided materially in the drainage and healing of the pulmonary abscess.

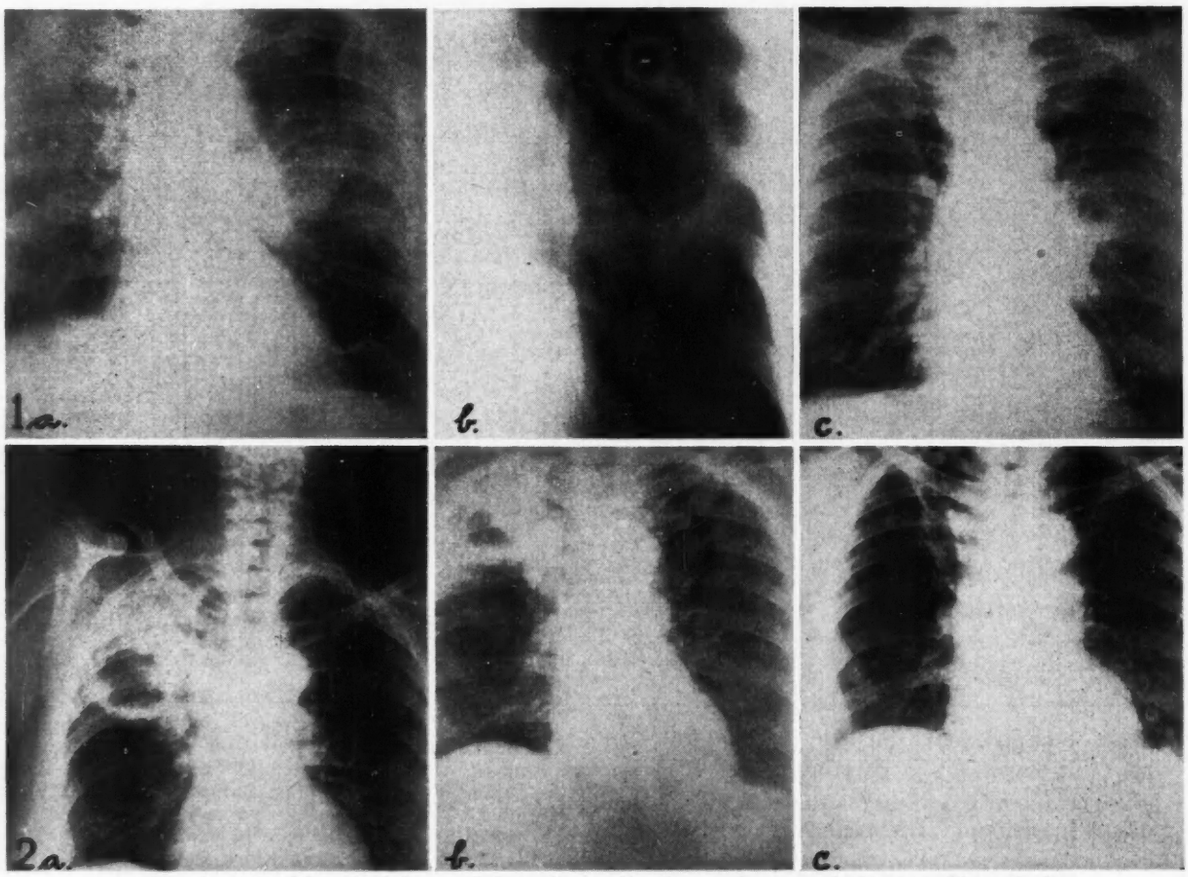

Fig. 1a.—23rd hospital day and day of complication and onset of abscess. Note shadow in the left hilar area. **Fig. 1b.**—35th hospital day and 12 days after onset of complication with abscess. Note ragged abscess in the left hilar area shown by tomogram at 8 cm. level. **Fig. 1c.**—97th hospital day and 74th day after onset of complication with abscess. Note increased left hilar markings but no abscess. An x-ray taken on the 116th hospital day shows the left hilar markings to be practically normal. **Fig. 2a.**—X-ray on admission and approximately seven days after onset of abscess formation. Note dense shadows and ragged abscess area in the right upper lung field. **Fig. 2b.**—12th hospital day. Note decrease in dense shadows and abscess area. **Fig. 2c.**—40th hospital day. Note streaking only toward right upper lung field from the hilar area. X-rays of a later date showed this to have subsided in great degree.

DISCUSSION

The treatment as outlined in the previous section and exemplified in the case reports, attempted to do five things: combat infection; relieve broncho-spasm and œdema of the respiratory passages; liquefy tenacious mucoid secretions; allow the liquefied tenacious secretions to flow out by gravity; reinforce these by the expulsive force of coughing. These steps were fulfilled by instituting the following measures: using antibiotics; employing broncho-dilator vaso-constrictor drugs; using an expectorant mixture; postural drainage; encouragement to cough.

In the past the medical management of pulmonary abscess often met with failure. Aerosol therapy with broncho-dilator and vaso-constrictor drugs has been added. The authors feel this has been of considerable value. Epinephrine 1% may be employed to give a quick effect, which can be prolonged by incorporating ephedrine 1% or neosynephrine 1%. Previous publications[2, 3, 5] have stressed the principles upon which this therapy is based. The application by aerosol of the broncho-dilator and vaso-constrictor drugs direct to the affected areas relieves the œdema and obstruction. The patients cough more easily and expectorate their retained secretions with less effort. This also permits the aerosol penicillin to be more effectively applied topically at this diseased site.

It is claimed by some[1] that penicillin inhalation can be little more than a minor aid to treatment in this condition. It is interesting that Segall and Ryder[8] in most of their 11 cases, did not employ intramuscular penicillin along with penicillin aerosol. They obtained clinical and radiological cure in all cases.

Bronchoscopic and bronchographic examinations were done before and after discharge from hospital to rule out bronchogenic carcinoma in all cases in this report.

CONCLUSIONS

Prior to the use of penicillin and aerosol therapy as outlined the treatment of non-tuberculous suppurative pneumonia frequently required early thoracic surgery. The basis of this treatment was drainage.

The employment of medical treatment alone, incorporating aerosol broncho-dilator and vaso-constrictor drugs, together with penicillin intramuscularly and by aerosol, lead to a satisfactory clinical and radiological recovery in eight consecutive cases of lung abscess.

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1390 Sherbrooke St. W.

A TWO-WAY T-TUBE FOR CONTINUOUS POSTOPERATIVE PERFUSION OF THE BILIARY TREE

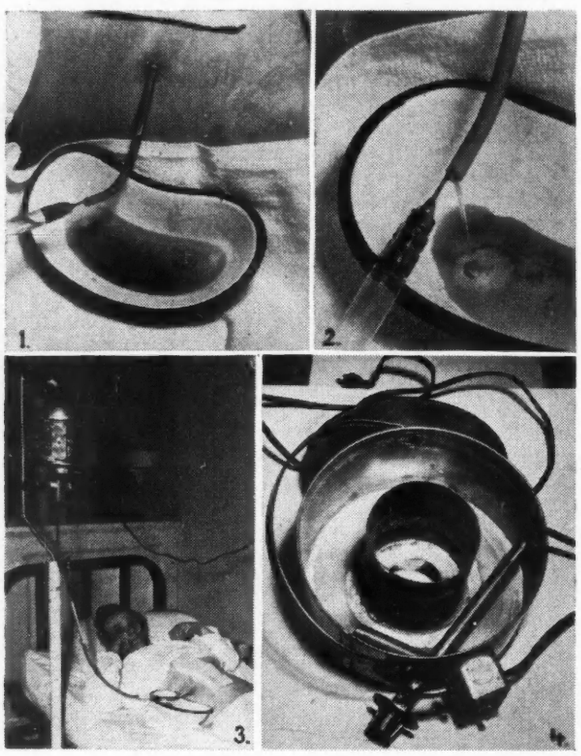
Dean Macdonald, M.D., F.A.C.S.

St. Catharines, Ont.

REALIZING the frequent beneficial effects of heat when applied to many functional and structural body changes, particularly those of inflammatory origin, it was hypothesized that if sufficient heat could be applied in a simple and practical way directly to some of the postoperative biliary conditions, an improvement in the long range results might be expected. This method would be applicable, of course, only to those patients in whom a drainage tube remained in the biliary system after operation.[1] Such a thought has been put to the clinical test, using heated fluids and the conventional drainage tubes, and has been briefly reported elsewhere.[2, 3] Those results warranted a more extensive clinical trial and experimental work. The present report concerns some of that clinical work. Although this is not extensive, it has suggested enough to warrant this presentation, so that a further and more critical evaluation of its possibilities might be made by other workers. Lack of facilities makes it imposible to carry out the investigative work which is a necessary part of either deductive or proved conclusions. For example, among the factors which should be proved experimentally before the final clinical value can be discussed, are: (1) exactly how far peripherally the fluids extend using different perfusion pressures; (2) the damage, if any, done by the heat and the increased pressures; (3) the rate of heat loss between the portal area and the furthest point reached; (4) the effect of heat on the pancreas; and (5) the effect of dif-

ferent degrees of cold on the metabolism of the normal and abnormal liver and pancreas. This latter point may be of the greatest importance, particularly in reducing the pancreatic blood supply before second stage resections, and even in the rate of growth of malignancy.

While using the usual T-tube or catheter, it became obvious that an improvement in the method of introduction and distribution of the heat was necessary. A two-way T-tube, containing an inflow and an outflow channel, was therefore devised, after the same principle had been proved satisfactory by inserting a very small catheter through the lumen of a large T-tube. The use of this tube seemed to greatly increase the area covered by the ingoing fluids as determined by cholangiography, and it therefore probably also increased the area influenced by the heat transported by the fluids, particularly when fluids were introduced by means of a continuous flow. Such a flow also increased the cleansing properties of the procedure (Figs. 1 and 2). It also soon became evident that the practical and clinical value of the method depended upon the maintenance of a constant and controlled temperature, as well as upon a minimum of an attendant's time. This was achieved by heating the fluid in a thermostatically controlled water bath, and introducing it through the small inflow section of the two-way T-tube, the rate being regulated by the usual intravenous apparatus.



Figs. 1. and 2.—The two-way T-tube leaves the abdomen lateral to the vertical incision. Note the silk suture holding the tube in place. An intravenous needle (size 16 or 18) is gripped firmly by the small calibre of the inflow channel. Note also the debris which has been washed from the ducts three weeks after operation. In (2) "close-up" of the end of the tube shows the two openings clearly with the perfusion fluid running. **Fig. 3.**—The perfusion apparatus. The vacuum drop permits continual observation of the flow. The patient can slow or stop the flow if it produces pain. The open end of the intravenous bottle is seen projecting from the under surface of the heating chamber with the vacuum drop connected. **Fig. 4.**—Illustrates the interior of the heating apparatus and shows the water chamber surrounding the central compartment which holds the perfusion fluid flask. Also shown are the "off and on" switch, the thermostatic control in and out of the heating chamber and the heating element in the water chamber.

TECHNIQUE

A "Baxter" 500 c.c. jar of intravenous 5% glucose in distilled water is placed, upside down, in a water bath heated by thermostatic control. The usual intravenous continuous drip "set-up" is used and an intravenous thermometer is inserted into the continuity of the tube, as close to the abdominal entrance as possible. The average temperature at this point approximates 120 to 130° C. and has been as high as 140° C. An intravenous needle, size 18, is inserted into the small inflow channel of the tube (Fig. 1). The outflow empties into a white basin placed at the side of the patient. This allows a clear observation of the outflow fluid with its ductal debris. Morphine is sometimes required to increase sphincteric resistance and thereby improve the intra-ductal circulation of the fluid. It is hoped that future tubes might have separate inflow and outflow flanges at the outer end.

Although the following brief résumé of case histories does not permit positive and scientific conclusions, it is thought that they contain sufficient "circumstantial" evidence to warrant the suggestions contained in the general conclusions. Most of the results are thought to have been better than those which might have followed medical treatment and/or biliary drainage without perfusion. Nevertheless, not all cases had as happy endings as those reported. The "poorer" results were often associated with those cases in which perfusion could not be performed regularly.

CASE 1

Mrs. B., aged 54. Cholecystectomy performed elsewhere four months previously. Operation for repair of traumatic stricture of common bile duct. Slow perfusion with fluid at 105° C. started on the third postoperative day. Temperature gradually raised to 125° C. and continued daily for hospital stay of two weeks. Continued at home intermittently for two months using distilled water whose temperature ranged from 110 to 120°. Clinical improvement following surgery was more rapid than usual. Jaundice, which had been present for the entire interval of almost four months, disappeared clinically in one week, and the blood bilirubin returned to approximately normal (1.1 mgm. total). Preoperative readings averaged (indirect) 27.4 mgm. Obstruction had been complete by laboratory findings.

CASE 2

Mrs. F., aged 56. Common bile duct cut across completely during difficult cholecystectomy. Anastomosis easy and satisfactory but exploration of common duct was actually "forgotten". Postoperative x-ray studies revealed normal width of duct at anastomotic line, but three calculi were plainly visible in the terminal section of the duct. These were much too large to pass the sphincter. Following two months' perfusion, using distilled water (115 to 125°) only one calculus shadow could be seen. "Dissolving" agents, other than heated fluids were not used.

CASE 3

Mrs. S., aged 51. Cholecystectomy five years previously. Preoperative diagnosis: common duct calculi. Surgical diagnosis: fibrosing pancreatitis producing intermittent and incomplete states of common duct obstruction. Pain was absent during two months postoperative perfusion. Pain returned when perfusion was stopped for one month, and disappeared when perfusion was again started. Temperature 110 to 130°.

CASE 4

Mr. M.M., aged 38. Diagnosis: severe infectious hepatitis. Medical treatment for two weeks ineffective. Signs and symptoms which were suspicious of common duct obstruction then became apparent. Surgery revealed a non-obstructed common duct. Liver biopsy showed "focal necrosing hepatitis". This patient was very sick. His clinical recovery following perfusion twice a day was unusually fast and astounded all who saw it. The heated fluids reached a thermometer temperature of 135° C. The preoperative medical therapy was not changed following operation.

CASE 5

Mr. G. H., aged 46. Three previous operations on biliary tract. All performed elsewhere. Preoperative diagnosis: incomplete common duct obstruction, etiology undetermined. Operative diagnosis: chronic fibrosing pancreatitis. This was substantiated by postoperative x-ray studies. Perfusion daily for one month. Freedom from symptoms, for first time in five years, has now lasted for over two years.

CASE 6

Mrs. W., aged 69. History of biliary disease for forty years. Jaundice present for one month. Due to a very recent coronary thrombosis, plus diabetes (hepatic?), plus hypertension, plus general physical decline during past year, the surgical risk was not good. Pre- and post-operative diagnosis: complete inflammatory and calculus obstruction of common bile duct. Recovery following daily perfusion for two weeks was exceptionally fast, and the improvement in the cardiac status was also remarkable.

CASE 7

Mrs. S., aged 32. Medical therapy for so-called biliary dyskinesia unsuccessful for two years. Because of continued colic, the diagnosis was changed to calculus disease . . . in spite of normal x-ray studies. Biliary tract essentially normal at operation. A small mushroom catheter was placed in the normal gallbladder. Postoperative x-ray studies revealed a narrow, short, twisted, thread-like cystic duct. Postoperative colic as severe as before operation, when catheter was clamped. The relief of symptoms was marked following postoperative installation, through the gallbladder catheter, of fluids heated as high as 140° for one week.

CASE 8

Mrs. W., aged 26. Nine pigment calculi removed from common duct at cholecystectomy. Postoperative x-ray studies revealed one square negative shadow at the beginning of the common bile duct. This could not be seen following three weeks' irrigation with tap water (130° C.) followed by equal parts of ether and alcohol, at two day intervals.

DISCUSSION

In Figs. 1 and 2 the return flow is seen to contain much sediment and debris. These fragments are potential common duct calculi. Whether such material will leave the bile ducts until the pressure in the common duct is greater than the vertical height of the T-tube is a debatable point. However, the fact that this material can be washed from the common duct weeks after the ordinary drainage has been instituted, and at a time when it is considered that the tube is ready to be removed, would seem to be sufficient proof that much debris does remain in the duct postoperatively, either with or without the usual drainage. This seems to indicate, therefore, that a discussion regarding a possible improvement in the present drainage methods is justified. It is suggested, and evidence is presented to indicate, that continuous perfusion might be a part of such an improvement.

Several attempts have been made to fragment calculi remaining in the common bile duct postoperatively, using equal parts of ether and alcohol, as advocated by Pribram. I have never had any success with this method until the use of the two-way T-tube as reported in Case 8, in which instance, a negative shadow of a calculus lying against the end of the tube, which was clearly seen before the slow instillation of equal parts of alcohol and ether, could not be seen afterwards. The outflow channel seems to allow a vent-like action which reduces the greatly increased intra-ductal pressure and pain resulting from the vaporization of the ether. The decreased pain may also be partly due to the small amount of solution used, and the slowness of the injection, both of which are the result of the small inflow channel.

Another interesting "by-product" of this study was the investigation of (1) the effect of different temperatures on the tone of the sphincter, and (2) the mechanics and radiation of ductal pain as produced by artificially increased intra-ductal pressures. Briefly, the results indicated that heat reduced sphincter resistance as determined by the choledochometer,[4] and that cold fluids gave variable results but, for the most part, produced a dull ache, without tenderness, in the high midline of the abdomen. Increase in the intraluminal pressure produced pain in the same area which radiated straight through to the back and was accompanied by

nausea and/or vomiting, an increase in the pulse rate, and an "up and down" change in the blood pressure. Electrocardiographic tracings did not accompany these observations, but in experimental animals the electrocardiogram has produced tracings consistent with coronary insufficiency and even of myocardial infarction (coronary thrombosis).

SUMMARY AND GENERAL CONCLUSIONS

A two-way T-tube is described. This is used for perfusing the postoperative intra- and extra-hepatic biliary system with fluids heated by thermostatic control. The inflow and outflow channels seem to make continuous perfusion a practical procedure of clinical value. Some of the advantages of such a procedure are briefly discussed. It is suggested that one of the principal requirements of successful biliary surgery, namely, the establishment and continuance of a free and uninterrupted flow of normal bile into the intestinal tract, is more likely to be fulfilled by this method of irrigation than by the present methods of "overflow" and "uphill" drainage. Nor do the present drains always produce a sediment-free duct. Using continuous perfusion, a common duct drainage tube is made to serve a definite purpose and to assume an active function, rather than remain as an inactive overflow spillway. It is also suggested that the heat so applied might aid in the dissolution of some of the hepatic, pancreatic, and common bile duct disease remaining postoperatively.

It is also suggested that this tube permits the application of heat to the interior of the liver in such quantity and quality that it might serve a very definite and helpful purpose in that large group of the hepatidites, which are not associated with the extra-hepatic ductal obstruction, *i.e.*, the so-called "medical" liver diseases.

Of added interest is the possible improvement in the dissolution of common duct calculi remaining after operation, particularly the pigment (non-infective) calculi. Using the one-way tube, this is not a satisfactory procedure, nor is it without danger. The two-way tube permits the slow injection of very small amounts of solution through the small inflow channel, while the larger outflow channel probably acts as a vent to reduce the increased intra-ductal pressure and pain resulting from the vaporization of ether, when the latter is used. There is also evidence to indicate that heat alone can fragment pigment calculi remaining after operation (Case 2).

Appreciation is expressed to Mr. F. J. Wallace of The American Cystoscope Makers, Inc., New York, for the manufacture of this tube.

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12 King Street.

THE USE OF RADIOACTIVE IODINE IN THE DIAGNOSIS OF HYPER- AND HYPO-THYROIDISM*

W. F. Perry, M.A., M.D., C.M.† and J. P. Gemmell, M.D., M.R.C.P.(Lond), F.R.C.P.[C.]‡

Winnipeg, Man.

AT present several aids are available to the clinician in the diagnosis of thyroid disorders. One of the most specific is the estimation of the amount of protein-bound iodine in plasma, which has been shown to be usually a reliable index of thyroid function.[1, 2] However, this determination is analytically difficult and time-consuming. Within recent years several groups of investigators have reported on the use of radioactive iodine. Using this isotope the ability of the thyroid to take up iodine[3, 4, 5] or the amount excreted in the urine over a known period of time may be estimated.[3, 6, 7, 8] The difference between the dose given and the amount appearing in the urine has been taken as an index of the activity of the thyroid gland. There are also recent reports[9, 10] on the amount of the isotope present in the blood 24 hours after a dose of radioactive iodine. This is taken as a measure of the rate of secretion of thyroid hormone by the gland. By measuring the excretion of radioiodine at intervals over a 24 to 48 hour period and plotting such values Keating and his collaborators[11] have derived an equation and from it have calculated certain rates. These are claimed to represent the rate of accumula-

* Contribution from the Department of Physiology and Medical Research and the Department of Medicine, University of Manitoba, and from the Department of Medical Research of the Winnipeg General Hospital, Winnipeg, Canada.

† Assistant Professor, Department of Physiology and Medical Research.

‡ Assistant Professor, Department of Medicine.

tion of iodine by the thyroid gland and the rate of excretion in the urine. These calculated values have been shown to be remarkably different in hyper-, hypo and euthyroid subjects.

Thus, although methods utilizing radioiodine appear to be as useful as plasma-protein bound iodine determinations in diagnosing thyroid disorders and are indeed capable of providing additional information concerning the behaviour of the thyroid gland, nevertheless their relative reliability has not yet been assessed, nor is it known which of the radioactive methods is the best suited for clinical use. With this in mind the study reported below was undertaken.

SUBJECTS AND METHODS

The subjects studied are described in Table I. They were divided into three groups based on clinical criteria, *viz.*, euthyroid, hyperthyroid and hypothyroid. The term euthyroid designates persons whose tissues at large receive the normal amount of thyroid hormone daily, irrespective of the anatomical state of the thyroid gland.[12] Clinical diagnoses were supported by observers other than ourselves.

The radioactive iodine obtained from the Chalk River Atomic Energy Project, was administered orally without carrier in 50 to 100 ml. of water; the container and mouth being rinsed with an additional 100 ml. of water. The subjects were fasting and remained so for one to two hours after the dose.

TABLE I.

DETAILS OF SUBJECTS

No.	*Age*	*Sex*	*Basal metabolic rate*	*Diagnosis*	
1	39	M.		euthyroid;	normal
2	22	M.		euthyroid;	normal
3	59	F.	−17	euthyroid;	arteriosclerosis
4	41	M.		euthyroid;	normal
5	47	M.		euthyroid;	normal
6	43	M.		euthyroid;	duodenal ulcer?
7	68	F.	+12	euthyroid;	non-toxic adenoma arteriosclerotic heart disease
8	55	M.	+8	euthyroid;	anxiety state
9	31	F.	−24	euthyroid;	hirsutism
10	38	M.		euthyroid;	dermatitis
11	21	M.		euthyroid;	small non-toxic diffuse goitre
12	23	F.	−8	euthyroid;	diabetic; diffuse non-toxic goitre
13	65	F.	−14	euthyroid;	carcinoma of thyroid
14	66	F.		euthyroid;	carcinoma of thyroid
15	32	F.	+3	euthyroid;	carcinoma of thyroid
16	70	M.	−22	myxœdema;	arteriosclerotic heart disease
17	73	M.	−26	myxœdema;	angina; arteriosclerosis
18	33	F.	−34	hypothyroid;	
19	70	F.	−21	myxœdema	
20	79	F.	−8	myxœdema;	arteriosclerotic heart disease
21	65	M.		hypothyroid;	psychotic
22	45	F.	−44	hypothyroid	
23	31	F.	−41	hypothyroid	
24	58	F.	+31	hyperthyroid	
25	65	M.	+49	hyperthyroid	
26	44	F.	+64	hyperthyroid	
27	59	F.	+15	hyperthyroid;	recurrence
28	53	M.	+29	hyperthyroid;	exophthalmos
29	53	F.	+36	hyperthyroid;	auricular fibrillation
30	54	F.	+22	hyperthyroid;	toxic adenoma; auricular fibrillation
31	51	F.	+10	hyperthyroid	
32	48	M.	+18	hyperthyroid;	myasthenia gravis
33	44	F.	+17	hyperthyroid;	exophthalmos
34	23	F.	+30	hyperthyroid	
35	72	F.	+26	hyperthyroid;	toxic adenoma

The dose administered varied. In most cases it was 100 microcuries because in the determination of radioactive protein-bound iodine it was found this was the smallest dose that would give reasonably accurate counts in the plasma aliquots taken for analysis. In instances where thyroid uptake and urinary excretion only were considered a dose of 50 microcuries was sufficient and if urine excretion alone was to be measured a dose of 10 microcuries was adequate.

Protein-bound plasma iodine (PBI^{127}) was estimated by the method of Perry and Cosgrove.[2] Radioactive protein-bound plasma iodine (PBI^{131}) was estimated in plasma taken 24, 48 and in many cases 72 hours following the ingestion of 100 microcuries of I^{131}. The procedure was as follows: to 3-5 ml. of plasma was added an equal volume of 0.9% NaCl followed by 2 volumes of 12% CCl_3COOH (containing 3 mgm. KI/100 ml.). The precipitated proteins were centrifuged down and washed twice with 20 ml. of 5% CCl_3COOH (containing 1.5 mgm. KI/100 ml.), then redissolved in 10 ml. of 0.5 N.NaOH. The protein was reprecipitated with an equal volume of the 12% CCl_3COOH and washed once with 5% CCl_3COOH. The protein was then subjected to the same digestive and distillation procedure used in the estimation of the stable protein bound iodine.[2] To the resulting distillate was added 1 ml. of 1.5% KI followed by 1 ml. of 1% palladium chloride. The resulting precipitate of palladium iodine was filtered on to a disk of filter paper, placed in a holder and its radioactivity measured. A suitable aliquot of the dose of I^{131} given was subjected to a similar precipitation and counted. The results were expressed as a percentage of dose per litre of plasma.

In some cases the amount of radioactive thyroxine iodine in plasma taken 48 hours after the dose was estimated by a procedure similar to that of Taurog and Chaikoff.[13] Five ml. of plasma were extracted three times with 15, 10 and 5 ml. of butanol which removed the organic and inorganic iodine. The combined butanol extracts were shaken twice with 30 ml. of 5% Na_2CO_3 in 4 N.NaOH removing diiodotyrosine and inorganic iodine. The butanol (now containing thyroxine iodine) was evaporated to dryness and then subjected to the same digestive, distillation and precipitation procedures as for the protein bound iodine determinations. In radioactive measurements on plasma or butanol extracts counts on duplicate samples showed a maximal difference of 15%.

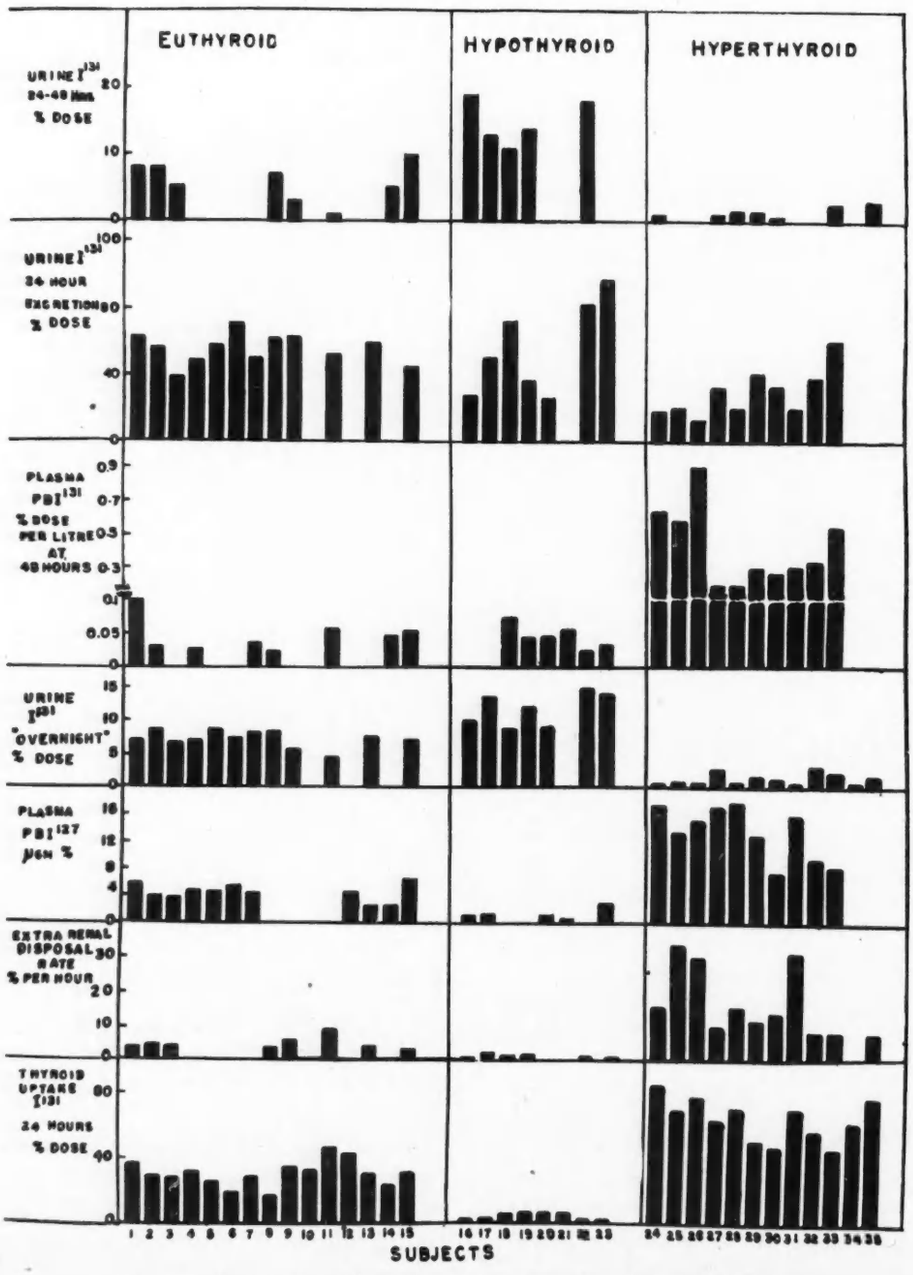
EUTHYROID
HYPOTHYROID
HYPERTHYROID
URINE I131 24-48 Hrs % DOSE
URINE I131 24 HOUR EXCRETION % DOSE
PLASMA PBI131 % DOSE PER LITRE AT 48 HOURS
URINE I131 "OVERNIGHT" % DOSE
PLASMA PBI127 µgm %
EXTRA RENAL DISPOSAL RATE % PER HOUR
THYROID UPTAKE I131 24 HOURS % DOSE
SUBJECTS

Fig. 1.—Comparison of various measurements of thyroid function.

The radioactivity of the urine was determined using the following procedure. After measurement of the volume of the specimen duplicate 0.5 ml. aliquots were carefully pipetted into small stainless steel dishes. To each dish was added one drop of 1.5% solution of KI and 0.2 ml. of $AgNO_3$ solution (containing 0.1 mgm. Ag per ml.). The samples were evaporated to dryness without boiling under an infra red lamp and counted. Following this an appropriate aliquot of the standard of I^{131} was added to the samples which were then redried and counted under similar conditions. The activity of the sample was expressed as a percentage of the dose. Counts on duplicate samples did not differ by more than 5%. The excretion of radioiodine was plotted against time and from inspection of the resultant curve the asymptotic amount was determined and designated the renal fraction. From this figure and the excretion curve certain rates were calculated according to the method described by Keating *et al.*[11] These rates were the disappearance rate of I^{131} from the blood; the renal excretion rate; and of particular interest, the extra renal disposal rate.

The "overnight" specimen of urine is defined as the urine excreted in the nine hour period commencing 15 hours after the dose. The percentage of the dose excreted in the overnight specimen was determined from the urinary excretion curve or from actual specimens.

The fraction of a given dose of radioactive iodine present in the thyroid gland 24 hours after the dose was determined by direct counting over the thyroid gland and eight inches above it, using a shielded collimated tube similar to that described by Ansell and Rotblat,[14] and Miller *et al.*[15] Comparisons were made to a standard solution of radioiodine in a glass container at the same distance from the counting tube. Corrections were made for general radiation from the body by doing similar counts over a part of the body remote from the thyroid, generally the thigh. Except in the case of hypothyroids the correction was of little importance. Duplicate counts agreed within 5% or less.

correlated very well. The 24 hour uptake separated the hypothyroid and euthyroid groups very sharply, but in two euthyroid subjects (Nos. 11 and 12) the uptakes approached the lower hyperthyroid values. The extra-renal disposal rate also sharply separated the hypothyroid and euthyroid groups and as well provided a good separation of the latter from the hyperthyroid group, with the exception of Case 11.

The PBI^{127} determinations, with the exception of two cases of thyroid carcinoma, provided a good differentiation between the three groups of subjects. The depressed values in two of the cases of thyroid carcinoma could not be explained on the basis of low plasma proteins,[2, 26] a condition which may cause low plasma concentrations of PBI^{127}.

The measurement of the overnight excretion of I^{131} provided a good separation of the euthyroid from the hyperthyroid groups but did not provide quite as clear cut a separation of the hypothyroid group from the euthyroids. These two latter groups were perhaps somewhat better separated as regards the amount of the isotope excreted between 24 and 48 hours after the administration of the dose. At this time the

TABLE II.

THE RADIOACTIVE PROTEIN BOUND PLASMA IODINE AT VARIOUS TIMES AFTER ADMINISTRATION OF I^{131}. (ALL VALUES EXPRESSED AS PER CENT DOSE PER LITRE OF PLASMA).

Euthyroid subjects				*Hypothyroid subjects*				*Hyperthyroid subjects*			
No.	*24 hours*	*48 hours*	*72 hours*	*No.*	*24 hours*	*48 hours*	*72 hours*	*No.*	*24 hours*	*48 hours*	*72 hours*
1	0.015	0.103	—	18	0.023	0.074	—	24	0.340	0.660	0.780
2	0.029	0.030	0.060	19	—	0.043	0.042	25	0.379	0.590	0.753
3	0.025	—	—	20	0.052	0.045	—	26	0.765	0.940	0.780
5	0.025	—	—	21	0.061	0.054	—	27	0.062	0.183	0.300
7	0.036	0.035	0.042	22	0.015	0.026	—	28	0.149	0.180	0.290
8	0.034	0.036	0.046	23	0.031	—	—	29	0.250	0.290	0.340
11	0.025	0.258	0.085					30	0.172	0.258	0.283
14	0.025	0.046	0.100					31	0.147	0.300	0.440
15	0.027	0.052	0.082					32	—	—	0.334
								33	0.350	0.530	—

RESULTS

In Fig. 1 is shown a comparison of the various measurements made in the three groups of patients. In considering the results in general it will be seen that the sharpest differentiation between the euthyroid and dysthyroid subjects is given by the 24 hour uptake of the isotope by the thyroid gland and by the calculated rate of extra-renal disposal of circulating iodine. These two measurements and the estimation of the stable protein-bound plasma iodine (PBI^{127}) difference between the hyperthyroid and euthyroid groups was less marked. It will be seen on the other hand, that measurement of the 24 hour excretion of radioiodine showed an overlapping of values in all three groups.

The concentration of radioactive protein-bound plasma iodine (PBI^{131}) of the three groups of subjects is shown in Table II. The plasma was examined 24 hours after the dose (100 microcuries) and in many cases 48 and 72 hours after as well. The 48 hour values are also

shown in Fig. 1. The results at all three times showed striking differences in the levels of PBI^{131} between the euthyroid and hyperthyroid groups, the concentration in the latter being usually 10 times that of the former. The concentration in both these groups also tended to increase with time. The hypothyroid subjects had measurable amounts of PBI^{131} at all three times examined and in amounts of the same order of magnitude as the euthyroid subjects. This was so despite the fact that they had low values for PBI^{127} and little or no detectable uptake of radioactive iodine by their thyroids.

In a few cases the radioactive thyroxine plasma iodine was determined in plasma 48 hours after administration of the isotope. The values are shown in Table III. The results

TABLE III.

PLASMA THYROXINE I^{131} CONTENT 48 HOURS AFTER DOSE

No.	*Diagnosis*	*PBI^{131} % dose/l.*	*Thyroxine I^{131} % dose/l.*	*Thyroxine I^{131} % PBI^{131}*
8	euthyroid	0.036	0.023	67
11	euthyroid	0.058	0.048	84
21	hypothyroid	0.054	0.033	60
22	hypothyroid	0.026	0.014	54
31	hyperthyroid	0.300	0.170	58
33	hyperthyroid	0.530	0.340	63

paralleled those for PBI^{131} in that the hyperthyroids had considerably more activity than the euthyroids and the hypothyroids apparently had labelled thyroxine circulating in the plasma to the same degree as the euthyroids. The fraction of the radioactive protein-bound plasma iodine present as thyroxine was similar in all cases studied.

DISCUSSION

It is important to note that for a preliminary evaluation of these tests the subjects were selected so that no cases where the clinical diagnosis was doubtful or controversial have been included. Thus the results obtained do not necessarily represent the findings in doubtful cases.

The above results indicate that in the use of radioactive iodine as a diagnostic aid in thyroid disorders certain measurements of the isotope are better than others when considered as to the ease of performance and the ability to differentiate the normal from the abnormal. One of these is the measurement of the amount of the isotope present in the thyroid gland 24 hours after the dose. Despite the inherent errors in the absolute measurement of radioactivity *in vivo* this determination would appear from our results to provide a good and very simple assessment of thyroid activity.

The rate of extra-renal disposal of circulating iodine also provides a sharp differentiation between hypo-, hyper- and euthyroid individuals. Assuming the extra-renal disposal is largely a thyroid phenomenon this measurement is a good reflection of the rate of uptake of iodine by the gland. However the calculation of the rate depends upon the analysis of an excretion curve which in turn is constructed by measurement of the quantities excreted in a number of urine specimens collected serially. The difficulties attendant upon accurate collection of multiple urine specimens even under ideal conditions militates against the usefulness of this procedure, good though it may be.

The measurement of the fraction of the dose excreted in the over-night period, *i.e.*, the period between 15 and 24 hours after the dose, would appear to provide a simple and reasonably accurate means of differentiating various degrees of thyroid activity. A similar proposal has been put forward by Arnott and Emery[8] who suggest measurement of the excretion between 12 and 24 hours after ingestion of the isotope. There is admittedly a tendency to overlapping of the values of the hypothyroid and normal groups on the basis of this procedure. Possibly examination of the amounts excreted in later conveniently timed periods would yield better results in these cases. For example, the excretion between 24 and 48 hours showed a better separation of the hypo- and euthyroid subjects.

The estimation of the amount of circulating PBI^{131} showed marked differences between hyper- and euthyroid subjects, especially when measured 48 hours after the dose. In addition in both groups there appeared to be a progressive increase in the amount present at each of the time intervals measured, *i.e.*, at 24, 48 and 72 hours. The few estimations performed of thyroxine iodine indicate that this fraction of the organic plasma iodine parallels the total organic or protein bound iodine and contributes to about the same degree in both groups. Paradoxically in cases with depressed or no thyroid function appreciable amounts of PBI^{131} and apparently thyroxine I^{131} are present in the plasma in amounts similar to the

euthyroids. This occurrence of PBI^{131} has also been noted by McConahey *et al.*[16] and Williams *et al.*[17] The reason for this is not at all clear, but it may be of significance that Morton *et al.*[18] have reported that the completely athyroid rat has the ability to synthesize small amounts of thyroxine and diiodotyrosine. Clark *et al.*[10] have recently reported on the measurement of isotopic plasma iodine 24 hours after a dose. Although the hypothyroid subjects investigated had measurable amounts of PBI^{131} these investigations showed that the ratio PBI^{131}/total plasma I^{131} provided a good separation of both hypo- and hyper-thyroid individuals from normals. While these workers used doses of the order of 0.5 to 1 or more millicuries their technique is doubtless adaptable to smaller doses of radioactive iodine.

Various factors and mechanisms must be considered which might make estimation of thyroid function by means of radioactive iodine not a strictly reliable index of the output of hormone by the gland. Any hyperplastic gland with a low iodine content will take up large quantities of ingested iodine. This has been reported by Keating *et al.* [27] and is possibly the cause of elevated uptakes in subjects 11 and 12 who were clinically not hyperthyroid. Such cases might also have elevated extra-renal disposal rates and low urinary excretions of I^{131}, *i.e.*, characteristics of the truly hyperthyroid individual. Similar misleading increases in the thyroid uptake of iodine have been reported with thiocyanate goitres[19] and in certain nodular goitres with hypothyroidism.[20]

Falsely low iodine uptakes by the thyroid and consequently high urinary excretions, conditions usually indicative of hypothyroidism, can occur if excessive quantities of iodides are being ingested or are circulating in the blood.[7, 21] In such cases the isotope is diluted by stable iodine and consequently less of the isotope is taken up by the thyroid.

Defective absorption from the gastro-intestinal tract and renal dysfunction will affect the behaviour of the thyroid gland toward radioiodine and give a false picture of its function.[7]

In all these conditions the determination of the stable protein-bound plasma iodine, PBI^{127}, may be expected to provide a truer index of thyroid activity. It is to be noted that falsely high values for PBI^{127} occur following administration of a variety of organic iodine compounds—most notably the dyes used in gall bladder visualizations.

Recent observations have shown that the administration of thyroid hormone causes an inhibition of the ability of the thyroid to pick up iodine and synthesize hormone.[5] This effect persists for some time after even a single dose of thyroid. If tracer studies are attempted on a euthyroid patient who has had recent thyroid medication, low thyroid uptakes of the isotope may be expected and hence hypothyroidism diagnosed. PBI^{127} values in such cases are also depressed.[22] Recent work by various investigators[23, 24, 25] has shown that administration of excessive amounts of iodide to both normal and hyperthyroid subjects will inhibit the organic binding of iodine by the thyroid, *i.e.*, depress hormone synthesis. If tracer studies are conducted on such subjects paradoxical results are to be expected.

It is hoped in the future to report on the use of I^{131} as a measure of thyroid activity in cases of defective cardiovascular and renal function and in cases where the clinical diagnosis as to thyroid function is uncertain or controversial.

SUMMARY

In a comparison of a number of measurements of thyroid function in a series of hyper-, hypo- and euthyroid subjects it was found that the measurements combining the sharpest differentiation with the greatest simplicity were the determination of the 24 hour thyroid uptake of radioactive iodine and the estimation of the amount of the isotope excreted in the urine in the period between 15 and 24 hours after administration.

The concentration of radioactive protein bound plasma iodine was found to be greater in hyperthyroid subjects at all times examined; however those with hypothyroidism had concentrations comparable to the euthyroid subjects.

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THERAPEUTIC USE OF LOCAL ANÆSTHESIA AS AN OFFICE PROCEDURE

A. Hurtig, B.A., M.D.

Ottawa, Ont.

THE doctor, in his office, is often confronted with patients who complain of either acute or chronic pain in the extremities and back, and quite often these pains form a rather bizarre pattern which make therapy difficult or impossible. There is a small group of these patients who, if certain indications are followed, may be permanently relieved of this pain by the injection of a local anæsthetic such as procaine or novocaine.

The use of local anæsthetics in supraspinatus tendinitis, some types of low back pain and in acute ankle sprains is not new, but it is amazing that very little interest in this form of therapy has been shown by the medical profession as a whole and it is to be deprecated that this form of treatment has fallen in disrepute by use in cases where it is definitely contraindicated. It also seems odd that no attempt has been made to postulate a basic pathology for these and other similar conditions which have responded to injection of a local anæsthetic agent.

Wells has shown that when the local blood supply is diminished by scar tissue, cell nutrition of that area is carried on by the seepage of plasma through the part. In the absence of red blood cells, oxidation is decreased and the local formation of carbon dioxide decreased. This leads to alkalinization of local plasma and possible precipitation of inorganic calcium carbonate and calcium phosphate.

Two points are worthy of note. (*a*) A similar process may be set up by local vasospasm and (*b*) the amount of calcification present is no measure of the pain suffered. For example, x-rays taken on the first day that a patient complains of pain in a calcified supraspinatus tendon show a calcification which must have been present for some time and has, heretofore, been asymptomatic.

Norwich states that if an acute (aseptic) inflammation causing increased blood supply is set up in an area of calcification the local metabolic rate is stepped up, more carbon dioxide is formed and there is a dissolution of calcium deposit. The local application of heat by various means ranging from a mustard plaster and electric hot pad to diathermy and ultra short wave physiotherapy achieves relief of pain by local or reflex vasodilatation.

The clinical papers of Leriche of France, Livingstone of Portland, Mandl of Jerusalem, Kuntz of St. Louis, Oschner and DeBakay of New Orleans and DeTakets and Gilbert of Chicago have brought to our attention the important relationship of peripheral vasospasm due to sympathetic imbalance and pain. They have proved that peripheral sensation transmitted to the cord and then to the sympathetic ganglia can cause localized vasospasm in the affected part and by means of identical sympathetic innervation from the ganglia involved cause vasospasm at a distance from the site of the original disease. This vasospasm in itself can cause severe pain out of proportion to the magnitude of the original tissue insult. In this manner, a sympathetic local cycle is set up which seems to continue uninterruptedly until broken. This has been postulated as the cause of pain in vasospastic conditions. Interruption of this sympathetic vicious cycle temporarily at the ganglion results in relief of pain, occasionally permanently, but usually for a period much longer than that of the local effect of the anæsthetic agent. As Pratt points out, this prolonged sympathectomy, long after the effects of the local anæsthetic agent have worn off, has never been satisfactorily explained. He suggests that the local anæsthetic breaks a synapse in the spasm pathway at the ganglion and that this synapse is slow to re-establish itself. If this were true, it could be postulated along the same line that the injection of the same agent peripherally, *i.e.*, at the site of the lesion, could act in exactly the same manner. The site of the lesion in the extremities is certainly more accessible to treatment, especially in the doctor's office than the sympathetic trunks or ganglia.

It is well known that a diseased blood vessel, due to its profuse sympathetic nerve supply, is, in effect, a diseased sympathetic nerve and can set up vasospasm in parts with a homologous sympathetic nerve supply.

The authors mentioned above have treated peripheral causalgic pain by stellate ganglion novocaine and/or alcohol block, sympathetic ganglionectomy, a severance of sympathetic fibres and, of late, others have used intravenous novocaine to cause a temporary or permanent break in the sympathetic vicious cycle thus causing a peripheral hyperæmia with dilatation of the local blood vessels. Those authors who use novocaine intravenously have proved that there is an increased seepage of plasma at any point of

vasospasm due to local capillary anoxia and this, in itself, causes a local hyperconcentration of novocaine which, by paralyzing the sympathetic nerve endings, causes a local vasodilatation.

It would seem feasible, therefore, that this type of treatment could be widened in its scope and remarkably simplified and the number of side effects reduced if the local anæsthetic is injected directly into the tender and painful area, and a temporary interruption in the sympathetic vicious cycle is effected. The site of the block is different from those above-mentioned, but, more important, it is more accessible and gives us a simpler procedure, with very few side reactions, that can be easily used in the doctor's office.

Lapidus, in 1943, used novocaine infiltration in the treatment of "acute tendinitis" around the shoulder, elbow, hip, knee and wrist. His treatments were limited to cases showing calcification on x-ray and he followed his novocaine infiltration with infiltration of warm normal saline and the procedure seems to have been used in hospital or in out-patient department. Most therapy heretofore has been aimed at flooding an area of tendon calcification with a local anæsthetic. As far back as 1908 Codman advocated injection of local anæsthesia in the therapy of periarticular calcification. In 1913, Flint of Yale aspirated deposits of calcium around the shoulder under local anæsthesia with good results. In 1938, Leriche and Young advocated the use of novocaine in such cases as a therapeutic procedure.

It is, however, common knowledge that the amount of calcification present is no criterion of the amount of pain the patient will have. Patients with exactly the same syndromes of pain about the shoulder, elbow, hip or ankle especially may show varying degrees of calcium deposit ranging from nil to large masses which must have taken months to lay down. This is most true in cases where there is no history of injury. A "supraspinatus syndrome" of 24 hours' duration with absolute inability to abduct the arm due to pain, with no previous history, may show no soft tissue calcification or so-called "massive deposition of calcium" anywhere about the abduction cuff. The physical findings are the same regardless of the amount of x-ray "proof", as are the results obtained by local anæsthetic infiltration which are immediate, prolonged, and, to both the patient and doctor, almost miraculous.

From the above data it seems logical to postulate the following:

1. A minor local injury, necrosis or disease in the muscle or tendon can set up a sympathetic vicious cycle causing local vasospasm at or close to the affected part.

2. This vasospasm, with its resultant partial tissue anoxia, will in time lead to deposition of calcium which will persist or increase until this local vasospasm is relieved by an acute attack of inflammation or by other means with subsequent dilatation. It seems reasonable to assume that the degree of calcification is no measure of the amount of pain the patient will have and that pain may occur before the deposition of calcium to the extent that it shows up in x-ray. It has been reported that 2.7% of all people have some degree of asymptomatic periarticular calcification.

3. The well-known analgesic effect of local heat and diathermy are obviously accomplished by superficial and deep vasodilatation respectively.

4. Local injection of an anæsthetic agent is a sure, quick method of obtaining local vasodilatation and absorption of the original irritating focus and its by-products.

5. It is, therefore, important that no epinephrine be used in the injection as has heretofore often been the common practice, as this procedure will obviously cause a certain amount of vasoconstriction and defeat the purpose at which we aim.

INDICATIONS

As has been mentioned above, the haphazard use of this form of therapy has led it into disrepute. An attempt is, therefore, made to lay down certain definite indications for this procedure.

(1) An accurate examination to rule out other causes of pain should be made. (2) There should be no evidence of infection in the affected part, either superficial or deep. (3) *Active* movement of the neighbouring joint or joints must be *painful* or impossible due to pain. The more acute the attack and the more severe the pain, the more dramatic the result. (4) *Passive* movement of the neighbouring joint or joints should be *painless.* It may take great patience to encourage the patient to allow such passive motion. (5) The points of tenderness to be injected must be *local* and *vocal* as opposed to *diffuse* and *sufferable.* (6) X-rays must always be taken to aid in accurate differential diagnosis. (7) X-ray evidence of calcification outside a joint is an indication for rather than a contraindication to this form of therapy. (8) A normal x-ray in the absence of inflammation and infec-

tion should encourage one to look for a local tender spot to inject. (9) In cases of recent injury, hypermobility of a joint after injection is a sign of severe ligamentous damage and is an indication for immobilization of the joint. Immediate use of this joint under local anæsthesia will cause even further damage. It is in exactly this type of case, especially in so-called "ankle sprains" that the teachings of Watson-Jones have not been observed. Poor results from injection treatment are inevitable and the memory of these disgruntled patients has caused many surgeons to drop this treatment in their practice completely. (10) An accurate knowledge of the anatomy involved is necessary, otherwise the doctor is truly shooting in the dark. (11) X-ray evidence of *intra-articular* disease is a definite contraindication to this form of therapy.

In the last three years, in my own private practice, I have successfully treated 75 patients with injection of a local anæsthetic agent with dramatic permanent results in these cases. In two other cases, the condition was aggravated, and in two more cases only partially relieved when a solution of procaine containing epinephrine was used by mistake. This would tend to confirm the accuracy of the theory outlined above. In 15 other cases the author's enthusiasm got the better of his good judgment and all the above criteria were not observed with uniformly poor results. Of six cases where x-rays were not taken and poor results obtained, intra-articular disease was demonstrated. These cases should obviously never have been injected.

METHOD

1. The site to be injected is painted with tincture of iodine and allowed to dry. In six cases the needle tracks showed a very mild superficial infection after the use of mercurial antiseptics.

2. One per cent procaine hydrochloride in distilled water or normal saline without epinephrine is the therapeutic agent used, loaded in a 10 c.c. syringe. A larger syringe is too cumbersome: 20 c.c. is the amount usually required. The same syringe is never used for more than one load of medication for the barrel usually contaminates the empty portion of the syringe if the fingers touch it.

3. The patient is always placed on the examining table so that any tendency to fainting can be easily overcome by momentarily dropping the head of the table.

4. A large intradermal wheal is raised over the affected area. One should now wait for two to three minutes and watch for a possible local allergic wheal. If this occurs the patient is obviously allergic to the agent used and the procedure should be discontinued at once.

5. An intramuscular needle is fixed to the syringe and the whole syringe emptied into the affected area while slowly advancing the needle. Alternate aspiration should be performed to prevent intravenous introduction.

6. The patient will usually complain of severe, acute, occasionally agonizing, fleeting pain when the needle enters the pathological site. This pain is much more severe than that caused by the introduction of the needle into the skin and is a reassurance to the physician that he has hit the right spot. It is wise to forewarn the patient regarding this effect or he will become severely alarmed. As large as possible proportion of the dose is deposited at this point.

7. The whole area is then massaged with a sponge dipped in alcohol until all tenderness disappears. The anæsthetic effect on the formerly tender spot has an encouraging effect on the patient. By the same manœuvre the iodine is removed to prevent iodine burn.

8. Active motion of the affected part through a complete range is then immediately required of the at first reluctant and then amazed patient for at least five minutes. This is often the first time that the patient has been able to move that joint since the onset of pain or since the recent injury. This phase of treatment is most important.

9. The patient is warned of a possible transient, acute exacerbation of pain without spasm within three or four hours. This pain is throbbing in character rather than constant, as was the first pain, and is due to the vasodilatation produced. An analgesic is prescribed to cover this period. Some patients have not experienced this return of pain at all.

10. The patient is warned that he must continue active movement of the affected part every hour on the hour, and is instructed to return to the office the next day to make sure that these orders are being followed.

Observing a large series of these patients shows a much greater proportion suffering this type of lesion about the convex aspect of the shoulder. Several names have been given to the syndrome, *viz.*, supraspinatus tendinitis, subdeltoid bursitis, abductor-cuff syndrome, etc. These conditions, with and without calcification, have been treated by deep x-ray, diathermy, saline irrigation, novocaine infiltration, local anæsthesia of the subscapular nerve, multiple needling and radical surgery by dissection. All these would seem to obtain the same effect by local vasodilatation and hyperæmia. This could be due to local temporary paralysis of vasoconstrictor impulses or temporary interruption of a sympathetic vicious cycle. Local infiltration of a local anæsthetic agent is an accurate immediate means of obtaining this end and should be attempted before more radical or lengthy procedures are attempted.

A common site is at the head of the radius or lateral aspect of the elbow joint. Pain at these points leads to the painful and disabling condition formerly known as tennis elbow. A piano teacher could not practice her profession; an accountant had to give up his only hobby—paddle tennis; a penitentiary officer could not grip or fire his revolver; a painter could not grip his brush properly; none could exert force turning a door handle. All these responded completely to one single treatment. Certainly this is an improvement over the textbook treatments of casts, pressure strapping or even resection of the head of the radius.

Four of the most dramatic cases treated were about the hip joint. The patients would not attempt to walk because of the severe pain in the lateral aspect of the proximal thigh with no antecedent history of injury. Local tenderness was discovered along the tensor fasciæ latæ.

Injection treatment immediately put an immobilized patient on his feet with no disability. A few cases like this and one is so sold on the treatment that restraint must be used or the proper indications will be disregarded.

About the knee, my results have not been good. This may be due to my own persistent difficulty in assessing cartilage and cruciate injuries. I inject no more knees and would counsel similar caution to others in treating this area.

Evidence of osteoarthritis in the back—present perhaps asymptomatically for years—makes one pause in assessment of the case of so-called "myositis" or "fibrositis" or "lumbago" or "acute back strain". If passive movement through a complete range is painless—and this is very difficult to assess—and all the indicated criteria are present, the treatment should be attempted. No harm is done and the possible end results justify the occasional failures.

SUMMARY

1. An attempt has been made to revive interest in an old but often neglected part of our armamentarium.

2. Definite criteria before its use are laid down.

3. The procedure is outlined step by step.

4. A possible physiological explanation is postulated.

150 Metcalfe Street.

PHENURONE AND HEPATITIS*

D. L. Lloyd-Smith, M.D., F.R.C.P.[C.]

Montreal, Que.

THE modern medical treatment of the epilepsies involves the use of a number of relatively new drugs, the toxic effects of some of which are not yet clearly defined.

Tridione, of particular value in petit mal and myoclonic epilepsy, has been found to produce neutropenia and agranulocytosis, glare phenomenon with photophobia, and drowsiness or lethargy,[1] and in rare instances, nephrosis.[2] Davis and Lennox[1] found paradione, which is closely related to tridione, to be associated with much less photophobia, and considerably less severe neutropenia than was tridione, when compared in similar patients, although paradione was slightly less effective. Mesantoin has been reported as leading to drowsiness, skin rashes and neutropenia;[3, 4] and acute aplastic anæmia was observed by England and McEachern during mesantoin therapy.[5]

Phenurone (phenacetylurea), one of the most recent arrivals in the field (introduced by Abbott Laboratories), appears also to have its specific disadvantages. Its chemical structure is related to that of dilantin and mesantoin: if the hydantoin ring is opened at a certain nitrogen-carbon linkage, the corresponding acetylurea is formed.[6] Gibbs, Everett and Richards[7] found it to be particularly useful in the control of psychomotor seizures, which are relatively poorly controlled by other medication. However, as they report, it not infrequently exaggerates previously existing personality disturbances. The result may resemble hysteria, schizophrenia, or psychopathic states, representing a wide variation, but in any one patient the abnormality may be fairly constant. Phenurone may also produce anorexia and nausea, feelings of weakness, headache, insomnia, palpitation and rash,[7, 8, 9] listed in order of decreasing frequency.

In view of the possible wide usefulness of phenurone and the necessity of assessing its toxic reactions, it was considered that the following case history, in which jaundice occurred in a patient who had been treated with the drug, would be of interest. Liver function tests were recorded. In this case, epileptic attacks had developed in adult life secondary to cerebral tumour.

CASE HISTORY

The patient, a well-nourished, white male, aged 42, was admitted to the Montreal Neurological Institute on August 17, 1949. He had been in good health until February, 1946, when he had begun to suffer from brief minor epileptic attacks consisting of simple rigid standing and staring, at first momentary, and later lasting five to ten seconds, of frequency about twice monthly and continuing over the ensuing years to the time of admission. In addition, he had had a major attack on at least three occasions over the past 3 years, consisting of falling, unconsciousness, and on one occasion tongue-biting.

Detailed description of the major attacks was as follows: *Aura.*—Subjective sensation of unsteadiness. *Pattern of attack.*—Generalized tonic spasm with falling, and unconsciousness lasting one to two minutes, and followed, on one or two occasions, by confusion, and once by automatism, during which he fought off persons who tried to assist him. *Post-ictal period.*—Amnesia for the entire attack. No evidence of aphasia, but following attack, speech became thick and mumbling.

About November 1948, after dilantin and phenobarbital had failed to control his attacks, he was placed on a regimen of mesantoin and phenobarbital (details of dosage not available). Several weeks later, the pa-

* From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

tient became ill with lethargy, general malaise, temperature of 101° F. and a faint rash. He was attended by several physicians, who excluded the common causes of fever of unknown origin. His temperature continued elevated between 100 and 103°, the rash becoming a generalized macular erythematous eruption. The anticonvulsant medication was suspected, and following cessation of the drugs the fever and rash quickly subsided.

In the last several months prior to admission, the patient had shown failing memory for recent events, and inability to concentrate, decreasing energy and drive, with increasing drowsiness. From the above description, it is evident that some of his seizures were suggestive of psychomotor attacks, and accordingly because of their persistence, two months prior to admission his medication was changed to phenurone 0.5 gm., three times daily, with phenobarbital ¾ gr., four times daily. In the last two weeks, because it appeared to be ineffective, the phenurone had been reduced by the patient and his relatives to 0.5 gm. once daily, and it was stopped entirely following the first consultation here on August 14, 1949.

During the last few weeks before admission, the patient had noticed slight dragging of his left leg periodically. His wife had noticed that he had a sallow complexion. On two occasions in the last 10 days the patient had been incontinent of urine during sleep.

General physical examination.—(1) Scleræ obviously icteric. Slight yellowish tinge to skin of abdomen. (2) Liver edge palpable two finger-breadths below the right costal margin, smooth in outline, of soft consistency and not tender. No other abdominal masses or tenderness.

Neurological examination.—(1) Difficulty in concentration. (2) Speech slow and hesitant, but not frankly dysarthric or aphasic. (3) Optic fundi showed questionable blurring and elevation of nasal margins of both optic discs. (4) Plotting of visual fields both by perimetry and on Bjerrum screen showed a small left homonymous upper field defect. (5) Slight weakness and slowness of voluntary movement of the left lower face. (6) Slight increase in deep tendon reflexes on the left side (left biceps, patellar and ankle jerks). (7) Gait showed a slight tendency to drag the left foot and to swing the left arm less than the right arm.

A clinical diagnosis of a right temporal neoplasm was made. This was supported by the results of ventriculography. At operation, a neoplasm was found involving almost the whole of the left temporal lobe, extending to the margins of the parietal and the occipital lobes. A removal was carried out, the histological sections showing the appearance of a piloid astrocytoma. The patient made an uneventful recovery from the operation, was discharged home on September 8, 1949, and has remained free of attacks to the date of this report (four months). The jaundice had disappeared clinically by August 27.

Discussion

In summary, a patient with focal cerebral seizures was treated for two months with phenurone and phenobarbital, at the end of which time he showed jaundice, which rapidly cleared following withdrawal of the phenurone, so that about ten days later the jaundice was not clinically appreciable. The liver edge was no longer palpable. There had been no previous attacks of jaundice. Infectious hepatitis is difficult to exclude, but there were no known other instances of jaundice in the family or in the community where the patient had been living, and the patient had received no intravenous injections or blood transfusions in the past year. Hepatic cirrhosis is unlikely from the negative past history, and the findings of the liver function tests.

Table I.

Liver Function Tests

Test	*Normal value*	*Patient; August 18*	*Patient; August 22*
Total serum proteins	6.9 to 8.5 gm. %	7.04 gm. %	
Albumen	4.4 to 6.0 gm. %	4.35 gm. %	.....
Globulin	1.5 to 3.0 gm. %	2.69 gm. %	
Bilirubin—direct	0.1 to 0.8 mgm. %	3.1 mgm. %	1.45 mgm. %
total	0.1 to 0.8 mgm. %	4.4 mgm. %	2.00 mgm. %
Alkaline phosphatase	3 to 13 units (King-Armstrong)	12.9 units	.....
Cephalin cholesterol flocculation	0 to 1+	4+	negative
Thymol turbidity	0 to 4 units	6.35 units	.....
Thymol flocculation	0 to 1+	trace	negative

There was no evidence of intra-abdominal neoplasm. The strongest indication that jaundice was due to a drug intoxication was its prompt disappearance when the drug was withdrawn. Further support is given to this explanation by the results of the liver functions tests (Table I), which show evidence of parenchymal liver cell damage (cephalin cholesterol flocculation and thymol turbidity tests), but no evidence of an obstructive element (normal alkaline phosphatase), and no evidence of long-standing liver disease (as judged by the plasma proteins). Flocculation and turbidity tests returned to normal within four days, and the serum bilirubin had markedly subsided. Urine tests for bile (modified Gmelin's test) gave a faintly positive result on August 18, and showed only a trace on August 22

Since this patient had had a previous toxic reaction to mesantoin, the possibility that he

presented an unusual degree of intolerance or an idiosyncrasy in relation to these drugs cannot be definitely excluded. Recently, however, another epileptic patient has been observed here who stated that a rather severe bout of jaundice had followed phenurone medication. Other drugs had been taken simultaneously and details are not available. Further, Davidson and Lennox[8] recently surveyed a series of over 100 cases of epilepsy treated with phenurone, and in one of their cases, liver damage was observed. They found phenurone had advantages over other medication, but noted the occurrence of side effects such as skin rashes, gastric disturbances, and personality disorders.* Gibbs *et al.*[7] also noted jaundice in one case of their series treated with phenurone, which subsided when the drug was stopped and reappeared when it was given again.

Experimental work at Abbott Laboratories as reported by Everett[10] indicated that in animals the liver plays some part in the destruction of phenurone. In view of this, although jaundice was not produced in animals with large dosages over long periods, the occurrence of jaundice clinically in a small percentage of cases, might not be surprising. This toxic effect of phenurone (phenacetylurea) may be related to the fact that in experimental animals, and probably in man, the liver is the site of production of urea.

Apparently then, it would be well to supervise patients taking phenurone by requiring them to report frequently during the first few months, for clinical examination and urinalysis. Before using phenurone, enquiry should be made to exclude a history of past liver disease (as well as of previous mental disorders).

SUMMARY

1. A case history is presented in which an epileptic patient having been treated with phenurone was found to have jaundice, which promptly subsided following withdrawal of the drug.

2. Liver function tests indicated that the jaundice was due to hepatitis presumably of toxic origin. There was no evidence for other common causes of jaundice.

* Abbott Laboratories, before making phenurone generally available, has carefully gathered results of extensive clinical trials, and report[9] that in the first 1,000 cases of patients treated with phenurone, on which data are available, some degree of liver dysfunction has occurred in about 3% of cases. Phenurone is still under investigation and is not yet available on the market.

The author wishes to thank Professor W. G. Penfield for his advice and for his permission to report this case.

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CLINICAL ASPECTS OF THE RH FACTOR*

Maurice Berger, M.D.

Winnipeg, Man.

THE Rh factor is a specific chemical substance present in human red blood cells. The white population can be divided into two broad groups in regard to the Rh factor: 85% who are termed Rh positive; 15% who are termed Rh negative.

The discovery of the Rh factor served to explain certain transfusion reactions and the pathogenesis of erythroblastosis fœtalis.

If an Rh negative individual is given a transfusion of Rh positive blood, antibodies may be produced whose specific function is to destroy Rh positive red blood cells. Therefore if further Rh positive blood is given to this Rh negative sensitized individual agglutination and hæmolysis of these Rh positive red blood cells will occur.

An Rh negative woman, whose husband is Rh positive and who is carrying an Rh positive fetus may also develop antibodies in her circulation whose specific function is the destruction of Rh positive red blood cells. The Rh substance or the Rh positive cells of the fetus may pass across the placenta into the mother's circulation and stimulate the production of antibodies. These antibodies in turn pass across the placental barrier into the circulation of the fetus and bring about destruction of the fetal red blood cells. The result is anæmia and jaundice. The infant in turn re-

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acts to this blood destruction by an attempt to replace its red blood cells and therefore in its circulation we may find many immature or nucleated red blood cells. Hence, erythroblastosis fetalis, or as the disease is also called, hæmolytic disease of the newborn.

From the above it follows that: (1) One should never give Rh positive blood to an Rh negative individual. (2) One should never give a blood transfusion or an intramuscular injection of blood to any female from infancy to the climacteric without first determining whether she is Rh negative or Rh positive. (3) One should never transfuse a woman with her husband's blood.

Consideration of the Rh negative woman who is pregnant involves the following: (1) Whether the husband is Rh negative or Rh positive. If he is Rh negative, all the children will be Rh negative and disease will not occur. (2) If the husband is Rh positive the first pregnancy will produce a normal offspring providing there is no history of transfusion or abortion. In the second pregnancy the offspring is usually normal. The chances of sensitization and erythroblastosis increase with repeated pregnancies. (3) If the husband is heterozygous, Rh positive, *i.e.*, if his genetic makeup is such that he can pass on either an Rh positive or Rh negative factor to his offspring, then there is always a possibility that the woman is carrying an Rh negative fetus. (4) Antibody studies in the Rh negative woman who is pregnant are important.

The infant will not have disease unless the mother has antibodies in her blood. Only 2 to 5% of pregnant Rh negative women produce antibodies. However an Rh incompatible blood transfusion will produce sensitization of the Rh negative woman in a much higher percentage than will pregnancy. The antibody studies should be done early in pregnancy. If antibodies are absent search for them should be repeated at 6 months and 8 months and 6 weeks after delivery as well for future prognosis. If antibodies are present early in pregnancy antibodies studies should be done each month to the 8th month and then every 2 weeks to term.

The Rh antibodies are of two types: (1) The saline antibody which agglutinates Rh positive red blood cells in a saline medium. (2) The albumen antibody which will *only* agglutinate Rh positive red blood cells in a protein medium such as 20% bovine albumen or plasma, etc.

What can be learned from the antibody titre during pregnancy in regard to prognosis? If there is not any history of transfusion or abortion or sick babies and if the titre of either saline or albumen antibody is under 16 it is likely that the baby will either be normal or only mildly ill. If you have an Rh negative woman who is pregnant and who has a history of abortion, transfusion or erythroblastotic infants, one should be prepared to treat the baby regardless of titre.

The diagnosis of erythroblastosis in the infant. One should always if possible be in a position to anticipate the birth of an erythroblastotic infant.

The most severe type of erythroblastosis fetalis is hydrops, where the fetus is grossly œdematous and dies *in utero* or shortly after birth. Sometimes the fetus is born in a macerated condition without œdema and occasionally appears normal outwardly.

Icterus gravis neonatorum is the commonest type. It may be mild, moderate or severe. Jaundice makes its appearance within 24 hours and in severe cases becomes rapidly intense, to a point where the infant may develop a greenish hue. The spleen is usually palpable and the liver may become enlarged. The hæmoglobin and red blood count are usually below normal. The hæmoglobin may be as low as 30% at birth in severe cases. There may be a large number of nucleated red blood cells in the stained blood smear and if this is so, the reticulocyte count is elevated. The blood bilirubin is higher than normal and rises rapidly. On the third day the more severely jaundiced infants may develop kernicterus, which is manifested by head retraction, and spasticity of the neck and limbs. Death may occur at this stage, but if these infants survive they may show mental defect, spasticity, strabismus, athetosis, etc. In the mild and moderate forms recovery may take place without sequelæ. Hæmorrhagic phenomena may occur with purpuric eruptions and hæmorrhages into the organs. Congenital anæmia of the newborn is a mild variety of hæmolytic disease where jaundice may not be very pronounced but an anæmia develops which becomes clinically manifest during the second week of life.

The differential diagnosis of erythroblastosis fetalis.—The use of serological tests has made the diagnosis of erythroblastosis fetalis easier. Perhaps the best and most rapid test for this purpose is the Coombs test or the anti-human globulin test. This test is simply a demonstration that the infant's erythrocytes are "coated" with immune anti-Rh antibody. The cells to be tested are washed three times in saline to remove serum. A 5% suspension of the washed cells in saline is made. A drop of this suspension is mixed with a drop of anti-human globulin. The mixture is left for a minute and then rocked gently. Agglutination will take place in from 1 to 5 minutes if the test is positive. A control may be set up with cells known to be unsensitized.

Other conditions may cause hydrops of the newborn infant. Syphilis may be a cause. Serology will help to differentiate. Other stigmata of syphilis will be present. The maternal Wassermann reaction is important. It may be associated with congenital malformations: or with prematurity. Hydrops may occur in the offspring of a woman who has been severely anæmic throughout pregnancy. The prognosis is usually good in these cases. Toxæmia of pregnancy may cause hydrops of the infant. Icterus gravis may be confused with physiological jaundice. In physiological jaundice the jaundice occurs after 24 hours usually from the 3rd to the 5th day, and is not as intense. The babies are well. The liver and spleen are not enlarged. The red blood count and hæmoglobin remain normal and fall slowly. There are only a few nucleated red blood cells in the smear and these quickly disappear.

Congenital obliteration of the bile ducts causes neonatal jaundice. The stools are acholic from birth but the jaundice does not make its appearance until the second week. There is not any anæmia or erythroblastoæmia. In icterus gravis one may get an obstructive type of jaundice with acholic stools. However there is a history of early onset of jaundice. The obstructive jaundice is thought to be due to liver destruction or pigment stone in the common bile duct.

Severe sepsis may cause neonatal jaundice. However jaundice appears later than in erythroblastosis, usually at the end of the first week of life and is preceded by several days of fever.

Familial acholuric jaundice may occur within the first few weeks of life producing a mild jaundice, splenomegaly and anæmia. The Rh serological tests are negative and there is increased red cell fragility.

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS

The most effective treatment at the present time for severe cases of erythroblastosis is exsanguination or replacement transfusion. The infant's red blood cells are withdrawn and are replaced by Rh negative red blood cells. The decision that has to be made at birth is whether to transfuse or not to transfuse. The factors which have to be taken into account are: (1) the history; (2) the antibody titre during pregnancy; (3) most important—the condition of the baby at birth.

The great majority of these babies look perfectly normal at birth. However examination of the infant's cord blood will show evidence of disease immediately. The cord blood should be checked for the following: (1) the Rh of the baby; (2) the sensitization of the red blood cells by the Coombs test; (3) the hæmoglobin and the red blood count; (4) the blood smear for nucleated red blood cells; (5) the blood bilirubin.

Criteria for replacement transfusion.—Cord blood: hæmoglobin under 15 grams; bilirubin over 4½ mgm. %; many nucleated red blood cells in the smear.

An enlarged spleen at birth is indication for replacement transfusion. Jaundice appearing within the first few hours after birth is also an indication for replacement transfusion.

Criteria for keeping the baby under observation and withholding treatment.—(1) No history; (2) the antibody in the mother not over sixteen during pregnancy; (3) cord blood-hæmoglobin 15 grams or over, the bilirubin under 4 mgm. %; (4) no enlargement of the spleen at birth; (5) jaundice is late in appearing, *i.e.*, after 12 to 18 hours.

The baby should be placed in an incubator at birth and one should wait for a few hours at least to allow it to recover from the shock of birth before instituting treatment. The replacement transfusion may be done by the umbilical vein within the first 24 hours. An average amount of blood removed is in the neighbourhood of 400 to 450 c.c. and the amount given is in excess of this depending upon the amount of anæmia present. Penicillin and sulfa should

be administered for several days after this procedure. Extra fluids should be given. The baby is allowed to nurse. Whether the infant is transfused or not transfused the hæmoglobin and red blood count are followed for six weeks. Transfusion is not given unless the red blood count falls below two million. Premature induction of labour is not indicated because it is not believed worth while to add the risk of prematurity to that of erythroblastosis.

The Rh hapten.—Recently Carter has suggested a new approach to the treatment of erythroblastosis fetalis. She has isolated a fraction from Rh positive red blood cells which she terms the Rh hapten. A hapten is a specific protein-free substance, which although associated with the antigen, is in itself non-antigenic and has the property of inactivating specific antibodies produced against the complete antigen. By injecting this Rh hapten into pregnant, sensitized Rh negative women she has been able to effect a reduction in antibody titre to zero in many cases. In addition normal babies have been born to hapten-treated mothers where severe erythroblastotics would normally be expected. Infants with severe erythroblastosis have been treated with hapten with good results in some cases.

The material is dissolved in absolute alcohol so that 1 c.c. contains 1 or 200 mgm. of hapten; 1 c.c. of hapten in alcohol is diluted in 10 c.c. of normal saline and is given into the gluteal muscle. Injections should be given as early as possible in pregnancy and continued at weekly intervals to term. Antibody studies are made at weekly intervals and the dosage of hapten adjusted accordingly.

This material is not available commercially and its use at the present time is experimental only. It will take many hundreds of cases to assess its real efficacy. Hapten is being prepared now in Dr. Chown's Rh laboratory in Winnipeg and is being used in selected cases. No definite opinion can be given at the present time as to its value.

I would like to mention briefly the occurrence of erythroblastosis in infants born to Rh positive mothers. These cases are due to sensitization to certain sub-types of the Rh factor and to unrelated antigens which are rare, such as the Lutheran, Lewis, Kell, antigens, etc.

1348 Main Street.

CASE REPORTS

PSEUDOMONAS ÆRUGINOSA DERMATITIS SUCCESSFULLY TREATED WITH STREPTOMYCIN

Maurice Saint-Martin, M.D.* and Gerard Lasalle, M.D.†

Montreal, Que.

Long before the discovery of *B. pyocyaneus* by Gessard in 1852, surgeons were well acquainted with the bluish-green discoloration of dressings of infected wounds. For some time, the pathogenicity of this organism was questioned; many workers considered it a curious and inoffensive microbe; others, a dangerous organism. Further studies revealed that both schools of thought were partially right. The organism being a facultative pathogen is often a saprophyte of the skin and intestines of man and animals, but can be the causative agent, alone or associated with other bacteria, of severe infections in immature or debilitated persons; and, following a traumatism or another infection, *Ps. æruginosa* may evidence a very marked pathogenicity.

Although involved in infections of various organs, its more common manifestations are infections of wounds and suppurative conditions of the middle ear. Callaway[1] and Sulzberger[2] have reported *Ps. æruginosa* infections of the ear canal successfully treated with topical application of streptomycin. We present a report of a case of acute eczematous dermatitis of the ear canal rapidly cured by this same treatment.

Miss R.L., aged 21 years, suffering from bilateral lesions of the ear canal, was examined July 30, 1948. These lesions had started at the end of the preceding May with a painless otorrhœa, followed by a dermatitis which gradually extended to the ear, scalp and inguinal and sub-mammary regions. The clinical diagnosis was acute eczematous dermatitis of the ear canal. The adjacent lesions were designated as pyodermatitis.

The patient seemed particularly concerned regarding the condition of her ears which did not improve in spite of numerous treatments: ear drops, wet dressings, hydrogen peroxide, penicillin intramuscularly and topically, tyrothricin, etc.

As the pus was yellowish-green, an infection due to *B. pyocyaneus* was suspected. In fact, pus from both of the ears gave a pure growth of *Ps. æruginosa.* This organism was highly virulent, as 1 c.c. of a 24 hour broth culture, injected intraperitoneally in a guinea pig, killed the animal in less than twenty hours. The autopsy showed the presence of a gelatinous œdema at the site

* Chief Bacteriologist, Division of Laboratories, Quebec Ministry of Health.

† Assistant in the Service of Dermato-Syphilography, Verdun General Hospital.

of inoculation, a peritoneal exudate and punctiform hæmorrhages of the stomach and intestines. *Ps. æruginosa* was isolated in pure culture from the peritoneal exudate. Cultures on Sabouraud's medium were negative for mycelial elements. On the other hand, secretions from the patient's scalp, inguinal and submammary lesions gave pure cultures of *Staphylococcus aureus*, coagulase positive.

Since the lesion was bilateral, we thought it might be interesting to try alternative treatments. The left ear was treated with an aqueous solution of streptomycin containing 2,500 units per c.c. The right ear was treated with a 35% solution of B.Q.X. (sodium benzenoxydioxypyrolidiethanoate). After 48 hours, the left ear was markedly improved, but the right ear did not show any improvement. Specimens from the right ear gave a pure growth of *Ps. æruginosa*, whereas culture of secretions from the left ear showed a marked decrease in number of colonies. After 96 hours, the left ear was free from secretion, with the lesions in process of regeneration. As the condition of the right ear was not favourably modified, the treatment with B.Q.X. was discontinued. Bacteriological examinations, negative in specimens from the left ear, did not show any change in the number of colonies of *Ps. æruginosa* in those from the right ear. Consequently, streptomycin treatment was started for the right ear and, 72 hours afterwards, a clean-cut amelioration of the lesions with negative cultures was noted. The patient seen in February, 1949, is definitely cured of the eczematous dermatitis of the ear canals.

COMMENT

At the risk of stating a truism, we feel that every infection should be investigated to determine, if possible, the etiological agent involved. Particularly is such an investigation advisable in this era of chemotherapy and antibiotics. In order to avoid therapeutic failures, discrediting useful medications, it is important to recognize the micro-organism responsible for the infection and, in some instances, to determine its sensitivity to the drug used. In our case, using a tube-dilution method employed in the laboratories of D.V.A. hospitals, the pyocyaneus strain isolated was found to be streptomycin-sensitive inhibited by a concentration of 1 unit per c.c.* Using a paper disc method, no inhibition of this strain was noted with the 35% B.Q.X. solution. Tests of sensitivity to streptomycin were considered worthwhile, for some strains of *Ps. æruginosa* are streptomycin-resistant.[3]

There was a distinct advantage in securing a rapid cure in this case, because of the localization of the lesions in the ear canal and its possible extension to the middle ear. It is also important to use the antibiotic of choice, because streptomycin can sensitize the ear canal as well as any other skin surface.

Bacteriological examinations of specimens from the lesions permitted the observation of an interesting phenomenon of variation. The identification of *Ps. æruginosa* is largely based on its ability to produce a bluish pigment called pyocyanin. The means of differentiation is not altogether satisfactory because some strains do not produce this pigment. Certain factors, like symbiosis with Gram-positive cocci, bacteriophagic lysis, media containing antiseptics, etc., may cause this organism to lose its property of forming pigment. Aoki,[4] studying 50 strains of *Ps. æruginosa*, found 3 strains which produced fluorescin pigment but were unable to produce pyocyanin, and 8 others unable to form either of these pigments.

The two strains isolated before the treatment was begun had the morphology, physiology and biochemical features as described by Bergey.[5] After the B.Q.X. treatment, the strain isolated from the right ear was typical. On the other hand, the *Ps. æruginosa* isolated from the left ear was atypical. The following variations were noted: (1) rod forms had practically disappeared, to be replaced by filamentous forms; (2) the strain had lost its power to liquefy gelatin; (3) the organism could not produce pyocyanin. These characters were held despite three sub-cultures. Furthermore, passage through a guinea-pig showed that this variant had lost none of its pathogenicity.

SUMMARY

A case of acute eczematous dermatitis of the ear canal, caused by *Ps. æruginosa* and cured with streptomycin, is presented. The importance of recognizing the etiological agent of an infection to permit choice of the proper antibiotic for treatment, is discussed. A variant of *Ps. æruginosa*, the result of streptomycin therapy, is described.

We wish to thank Mr. M. H. McCrady, chief of Laboratories, Quebec Ministry of Health, for his co-operation in reviewing the manuscript.

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SALMONELLA MENINGITIS IN THE NEW BORN*

D. C. Metcalfe, M.D. and G. B. Wiswell, M.D.

Halifax, N.S.

From the year 1907 to the time of writing, 149 cases of purulent meningitis due to the Salmonella group of organisms have been reported in the literature. Of this number, only one case occurring within the first month of life has recovered. We wish to add a second case, due in this instance to *Salmonella typhimurium*, which has been successfully treated.

CASE HISTORY

F.R.S., a white male infant eleven days of age, was admitted to hospital on August 16, 1948, with the history of having passed a dozen or more loose green stools during the preceding twenty-four hours. Birth had apparently been normal. Birth weight was seven pounds, two and one-half ounces. The infant had been fed on the breast, with complementary feedings of a partially skimmed milk formula.

The baby weighed five pounds, twelve ounces. Tissue turgor was fair. No signs of parenteral disease were elicited. Routine blood counts and urinalysis on admission revealed no abnormalities.

Course in hospital.—The clinical course remained uneventful for the first four days, moderate diarrhœa being present. On the fifth day, temperature suddenly rose to 103° F., and examination disclosed a tense, slightly bulging fontanelle and slight convergence of the eyes, the infant being extremely irritable. The leucocyte count at this time was 23,000. Lumbar puncture disclosed a turbid, yellow fluid. The report on the fluid from the Provincial Laboratory was as follows: "Stained films of sediment show numerous pus cells chiefly polymorphonuclears, with Gram-negative bacilli characteristic of *H. influenzæ*". Accordingly, streptomycin was started, 125 mgm. intramuscularly q.3 h. along with sulfadiazine two grams orally, q.4 h. Anti-hæmophilus influenzal anti-serum (50,000 units) was administered intravenously. Vollmer patch test and presumptive Kahn were reported as negative. On August 22, the laboratory reported that culture of organisms obtained from the cerebro-spinal fluid resembled Salmonella. A stool specimen was sent for culture. The temperature had dropped to 99° F; the leucocyte count was 21,700.

On August 23, the laboratory reported that organisms isolated from the spinal fluid were definitely Salmonella. Sugar was reported as being absent, chlorides 640 mgm. %, protein 225 mgm. %, and the colloidal curve 22443332. On August 25, (tenth hospital day) sulfadiazine was discontinued at 60 grains. Temperature was normal; leucocyte count was 16,000. Four days later streptomycin dosage was reduced to 125 mgm. q.6 h. On August 31 (16th hospital day) the laboratory reported the Salmonella to be *S. typhimurium* with the following antigenic structure: (I), IV, (V) XII; 1; 1, 2, 3. (Typing by kindness of Dr. E. L. Barton, Director of Laboratories, Ontario Department of Health). Streptomycin was discontinued eight days later, a total of 14 grams having been given, and sulfadiazine was restarted, the cerebrospinal fluid findings remaining essentially unchanged. The clinical condition of the infant at this time appeared good, no neurological findings being present. On September 16 (32nd hospital day), the stool culture was reported positive for *S. typhimurium*. At this point diarrhœa ceased, not to reappear. Sulfadiazine was discontinued on September 26 (42nd hospital day) at 228 grains.

On September 30 a recrudescence of clinically active disease occurred, the temperature rising quickly to 104.4° F. Physical examination revealed the patient to be extremely irritable, with a high-pitched cry and deviation of the eyes to the right and upwards. The spinal fluid, which had been clear for the preceding week, was found to be turbid. Streptomycin was restarted intramuscularly, 125 mgm. q.3 h., along with oral sulfadiazine. The following day, streptomycin was begun intrathecally for the first time, 50 mgm. being given daily; intramuscular streptomycin was reduced to 50 mgm. q.3 h.

Prior to the recrudescence, cerebrospinal fluid cultures had been sterile for one week, but with the development of clinical signs of infection, positive cultures were obtained and persisted until October 10 (56th hospital day) when the cultures again became negative for Salmonella. Soon after the institution of intrathecal streptomycin, the clinical status improved markedly, and, with the exception of a short period of nystagmus on October 6, neurological signs were entirely absent. All streptomycin therapy was discontinued on October 12, at 4 grams, three sterile cerebrospinal fluid cultures having been obtained. However, the abnormal chemical findings of the spinal fluid persisted. Medical and neurological consultants concurred in the opinion that streptomycin therapy should be given another trial in view of the persistent spinal fluid abnormalities, especially the decreased sugar. Accordingly, on October 14, another course of streptomycin was undertaken, 25 mgm. being given intramuscularly q.6 h., and 25 mgm. intrathecally daily. The hæmoglobin level being at this time 61% (9.8 gm.) a series of three blood transfusions of 80 c.c. each were given over the following two week period. Spinal fluid cultures continued to remain sterile. On October 28 (74th hospital day) a normal sugar level of the cerebrospinal fluid was reported for the first time, and subsequent specimens continued to show normal sugar levels. On the 83rd hospital day, intramuscular streptomycin was discontinued at 3.9 grams and on the 92nd hospital day (November 15) intrathecal streptomycin was discontinued, 0.8 grams having been given. On November 30, lumbar puncture was performed for the last time; examination of the fluid disclosed essentially negative chemical and bacteriologic findings.

On December 4 (110 days after admission), examination revealed a bright and active, clinically well infant with no positive neurological findings nor physical signs of disease referable to any other system. Weight was ten pounds, one ounce. Hæmoglobin was 95%; leucocyte count was 10,500. The infant was discharged to its home.

A follow-up study was conducted two months after discharge. At this time the infant appeared normal with no physical signs of disease. Weight was now seventeen pounds, diet for age was being consumed, and there had been no recurrence of diarrhœa.

Epidemiology. — Investigation revealed that an outbreak of diarrhœa had occurred in a local lying-in hospital in which the patient had been born. Stool cultures in several of these cases were subsequently reported as positive for *S. typhimurium*. It was later ascertained that one death had occurred; post mortem examination revealed the cause of death to be purulent meningitis; culture of the meningitic exudate was reported positive for *S. typhimurium*. The source of this epidemic was not determined despite intensive investigation.

* From the wards of The Children's Hospital, Department of Pædiatrics, Dalhousie University.

DISCUSSION

The first report of Salmonella meningitis was made in 1907 by Ghon,[2] who reported on two cases. In the following three decades, sporadic cases only were encountered and recorded in the literature. Bahrenburg and Ecker,[3] reviewing the literature in 1937, commented on reports of 34 cases. In 1940, Ramon Guerra, Peluffo and Aleppo[4] collected 59 cases from the literature. In 1948 Henderson[5] made an inclusive review of the subject, recording 147 cases, including three of his own. In the summer of 1948 Schweig and Cameron[6] reported a case in a three-month old infant. Recently another case was added to the literature by Gauvreau and Morin.[7]

Etiology and epidemiology.—Contrary to the previous popular conception, it has been concluded that all types of Salmonella may at times produce pathological changes in man.[8] Those strains with the greatest tendency to produce septicæmia are more commonly encountered in cultures of the spinal fluid in cases of Salmonella meningitis. Thus the commonest types encountered to date in the spinal fluid have been, in order of decreasing frequency, *S. enteriditis, S. paratyphi B, S. havana, S. panama, S. typhimurium, S. choleræsuis,* and *S. paratyphi A.* The accepted pathogenesis for the production of meningitis includes the ingestion of virulent organisms, the occurrence of septicæmia, followed by the establishment of an acute inflammatory process in the leptomeninges which are predicated to form a focus of diminished resistance.

The disease is predominantly an affliction of infancy and childhood, only 12 of the recorded 149 cases having occurred after the age of 14 years. There appears to be little difference in sex incidence in infancy and childhood; most of the adult cases have occurred in males. The disease is more commonly encountered in late summer and early autumn, with the low point of incidence in winter. Most of the reported cases have been sporadic in nature. However, an epidemic occurred in Cuba in 1936-37 with 21 deaths. Another outbreak was reported by Guthrie and Montgomery[9] in 1939 due to *S. enteriditis* in which 12 infants were affected with no recoveries. Salmonella infections occur all over the world. More cases have occurred in Central America, Cuba and the southern United States than elsewhere, but isolated cases have been reported in more temperate regions of the United States and in Canada. Salmonella infection is due in most instances to consumption of contaminated food in which the organisms have had an opportunity to multiply; other sources of infection include contaminated eating and drinking utensils, polluted water, flies, and infected animals. Direct patient-to-patient transfer of infection is rare.

Pathology.—In early infancy, the lesions encountered at autopsy are generalized. The usual findings include thickening and congestion of the ileum; enlargement of the solitary lymph follicles, Peyer's patches and mesenteric nodes; injection of the colonic mucosa; and the presence of a thick yellowish green, purulent exudate covering the meninges, which are congested and œdematous. Other evidence of general septic infection is occasionally found in the form of pyonephrosis, cholangitis, brain abscess, otitis media or bone infections. Single or multiple abscesses may be found in almost any organ of the body. In the older age group, intestinal lesions are not of common occurrence, and suppurative meningitis is in many cases the sole lesion encountered

Clinical features.—The clinical picture, like the pathological one, varies with the age group affected. In both age groups the signs of meningitis may be present, including irritability or apathy, nuchal rigidity, positive Kernig and Brudzinski signs, but in the younger infants the earlier stages especially may be manifested only by head-shaking movements or evidence of ocular inco-ordination. In early infancy, also, enteritis is usually present and may dominate the clinical picture, particularly at the onset. Fever of some degree is almost always present in both age groups.

Diagnosis.—The diagnosis of a suspected case is confirmed or ruled out by diagnostic lumbar puncture and laboratory examination of the spinal fluid. The causative organisms may often be detected on direct smear and subsequently identified by cultural and serological methods. If enteritis is present, stool cultures positive for Salmonella may be obtained.

Prognosis.—Up to the present time, age has played an important rôle in assessing the prognosis of an individual case; in general, the younger the patient the more serious the outlook. Thus, in 50 cases occurring under one month of age, recovery occurred in only one. Our case brings the number of recoveries in the under-

one-month group to two. In the older age group the prognosis is somewhat more hopeful.

The type of organism is another important factor to be considered in the prognosis, some types having a much higher fatality rate than others. Thus *S. enteriditis* produces the highest case fatality rate, and this organism, as we have mentioned, unfortunately has the highest morbidity rate of the Salmonella group.

Treatment.—Prior to the sulfonamide era, therapy consisted of symptomatic and supportive measures. After 1939, when the sulfonamides came into general use, chemotherapy was utilized in many cases, sulfadiazine being used in the majority of instances, and happily the fatality rate declined sharply. In patients treated without sulfonamides the case fatality rate was 93.8%; when sulfonamides were used the case fatality rate fell to 47.4%. Penicillin, as might be expected, has proved to be of no benefit. Reference to the literature indicates that up to now little experience has been had with streptomycin; records of its use in four cases are available, two of which succumbed and two recovered. Blood transfusion in repeated small amounts as a supportive measure is often of value.

Sequelæ.—Post-meningitis residua may occur, as with other types of purulent meningitis. Facial palsies, paralysis of extremities, deafness, blindness and hydrocephalus have been reported.

SUMMARY

A case of purulent meningitis due to *Salmonella typhimurium*, with recovery following streptomycin and sulfadiazine therapy, has been presented. This case was of special interest because: (1) Salmonella meningitis is an uncommon condition. (2) This is the only case of meningitis due to *S. typhimurium* which has terminated in recovery. (3) This is only the second case of Salmonella meningitis of any type under one month of age which has been successfully treated. (4) Reports on the use of streptomycin therapy for Salmonella meningitis have been few in number.

A brief review of the literature has been attempted with a discussion of some of the salient features of the disease.

We would like to express our appreciation to Dr. D. J. MacKenzie, Director of Laboratories, Department of Public Health, Nova Scotia, for his valuable laboratory assistance.

Addendum.—Since preparation of this paper, a case of Salmonella Newport meningitis has been reported (L. N. Pearlman and A. S. P. Gordon, *Canad. M. A. J.*, **60:** 483, 1949) bringing the total number of all recorded cases of Salmonella meningitis to 150.

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THROMBOSIS OF THE INFERIOR MESENTERIC ARTERY

R. Huggard, M.D., F.A.C.S. and A. Herstein, M.D., M.R.C.O.G.

Vancouver, B.C.

The following case brings up some interesting points.

Mrs. H.W.H., a 20-year old primipara was admitted May 5, 1947, at 7.45 p.m. in labour. At 10.30 a.m. next day she was delivered of a normal female infant. On May 7 at 9.00 a.m., the patient complained of pain in the abdomen, was restless, pale and appeared quite ill, pulse 120, blood pressure 110/70. The abdomen was distended with shifting dullness in the flanks and right-sided shoulder pain. The white blood count was 29,000, 83% polymorphonuclears; urine, sugar ++, a few granular casts and some red blood cells (catheter specimen).

At this time the possibility of abdominal hæmorrhage due to internal uterine rupture was considered by one of us (A.H.). Dr. J. Harrison was called in consultation and this diagnosis was supported, and laparotomy was decided on. After transfusion of two pints of blood, the abdomen was opened by a mid-line incision below the umbilicus. There was an abundance of serosanguinous fluid. Uterus, tubes and ovaries were normal and consistent with an immediate post-delivery state.

The left colon varied from a plum colour through hues of black and green and this discoloration extended from below the rectosigmoid junction to the mid portion of the transverse colon. At this time she was seen by Dr. Huggard, who demonstrated that the inferior mesenteric artery was completely thrombosed which accounted for the gangrene of the left colon. At a viable level below the rectosigmoid junction, the colon was sectioned and the distal portion over-sewn and invaginated. After mobilization of the left colon, it was excised to a point of viability to the right of the mid portion of the transverse colon, and the proximal loop was brought out through the abdominal wall as a single barrel colostomy. After closing the peritoneum over the bed of the excised portion of the colon, the abdomen was closed leaving a Penrose drain in the pelvis. A further pint of blood was administered in conjunction with a 1,000 c.c. of 5% glucose water.

The patient received a further 1,000 c.c. of plasma the day following operation and her immediate postoperative course was relatively uneventful. Three days following the colectomy, the clamp was removed from the colostomy and satisfactory colostomy function was established within two or three days. The patient's progress continued to be uneventful until May 24, when she developed a pelvic abscess which drained without difficulty through what was left of the rectal pouch. On June 3, she developed an acute thrombophlebitis of the left leg. Anti-coagulant therapy was commenced in conjunction with the administration of tetraethyl ammonium chloride intravenously. The symptoms responded well to this therapy and on June 12, she was out of bed and walking about, temperature and pulse normal, a good appetite, and her abdominal wound well healed. The colostomy was functioning satisfactorily. At this time, it was agreed that any thought to re-establish intestinal continuity should be postponed for some months.

The patient was re-admitted to hospital on September 30, 1947, and placed upon an adequate preoperative regimen. It was thought that enteric continuity could be re-established by using the cæcum which had been noted to be somewhat elongated during the first procedure. It was not thought that the colostomy end could be brought down to the level of the rectal pouch owing to the shortness of the right colic artery. Further, if the end of the terminal ileum was to be used to establish continuity, at a later date it would be necessary to remove the right colonic segment in order to do away with a mucous fistula.

Accordingly, on October 11, under cyclopropane and curare, the following procedure was carried out. Using a generous low right rectus incision the abdomen was opened and after encountering a few troublesome adhesions the appendix was removed in order to make the cæcum available for anastomosis. A supravaginal salpingo-hysterectomy was done in order to provide more working room in the pelvis and to reach what was left of the rectal pouch. The cæcum was mobilized by an incision of the lateral gutter and with some slight difficulty brought down into the pelvis. What remained of the rectal stump was mobilized. At this stage, with the patient in the lithotomy position, a transverse perineal incision was made and the posterior vaginal wall was incised as far as the posterior fornix opening into the peritoneal cavity. The cæcum was grasped, and with what remained of the rectal canal, consisting of the anal canal proper and a small pouch of rectum, an end-to-end anastomosis was done having a diameter that would admit two fingers. A rubber tube was left through the anastomosis. The perineum was reconstructed and the abdomen was closed, the colostomy remaining *in situ* in order to allow for ample decompression.

The colostomy closed of its own accord after two weeks and she was discharged from hospital after twenty days. Further treatment has consisted of a dilatation every two or three weeks of the fibrous ring at the anastomosis which is within ample finger reach of the anus.

As of November, 1949, she has two bowel movements a day, her stools are well formed, she has put on weight, and is enjoying good health.

This case report is submitted to bring to attention two points.

1. The authors are not prepared to offer any theory to account for the onset of thrombosis of the inferior mesenteric artery following delivery, but we do suggest that the association of the trauma that occurs in childbirth, plus some change in intra-abdominal pressure, could be contributing features.

2. A technique has been described that can be used for re-establishing enteric continuity where a large segment of the left colon of necessity has been excised. One of us (R.H.) has subsequently used this method in three cases where segments of left colon were excised for chronic diverticulitis. In all four cases this procedure has proved to be satisfactory and it is submitted for consideration. At a later time, it is hoped that a series of cases may be reported where this technique has been applied.

ACUTE LEUKÆMIA TREATED WITH CORTISONE*

D. G. Cameron, M.D., M.R.C.P.(Lond.)†

Montreal, Que.

J.B., a 60 year old white woman was admitted to the Montreal General Hospital on December 7, 1949. She complained of weakness, headache, malaise, fever and pain in the back and legs. These symptoms had persisted for several months despite treatment with sulfa drugs, penicillin and chloromycetin. The past history, functional enquiry, social history and family history were not relevant.

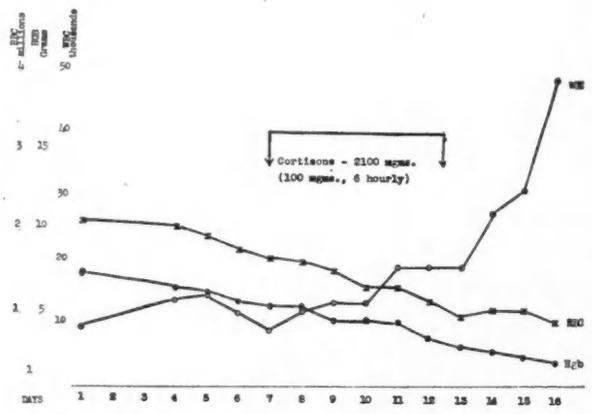
The patient was pale and appeared to be very ill. There were several petechiæ on the soft palate and small ecchymoses on the left breast and right shin. She complained of severe pain on pressure over the sternum and long bones. There was no adenopathy and the liver and spleen were not felt. Physical examination was not otherwise remarkable. Special investigations of interest were: red blood cells 2,100,000; hæmoglobin 7.2 gm. (46%); hæmatocrit 23%; red cell diameter 7.9 μ; reticulocytes $< 1\%$; platelets 160,000 per c.mm.; white blood cells, 8,800; differential leucocyte count, polymorphonuclears 48%; band forms 4%, eosinophiles 1%, lymphocytes 42%, monocytes 5%. The bleeding time, coagulation time and prothrombin time were all within the normal range. The capillary resistance test (Hess) was negative. A sternal puncture showed that the normal marrow cells were replaced almost completely

* From the Department of Medicine, the Montreal General Hospital.

† Senior Medical Research Fellow, National Research Council, Canada.

by masses of immature "blast" cells. The nature of these cells could not be determined with certainty but they were thought to belong to the myeloid series. A diagnosis of acute leukæmia was made.

2,100 mgm. of cortisone was given by intramuscular injection in doses of 100 mgm. every 6 hours. On the second day of treatment the patient gained 3 lb. in weight and slight œdema appeared over the dorsum of her feet. Her weight remained steady on subsequent days and the œdema did not increase. There was no change in blood pressure. On the third day she said she felt "easier" but her condition deteriorated relentlessly. On the fifth day ecchymoses appeared at the sites of the needle punctures and a sharp epistaxis was controlled by cautery. On the sixth day, the temperature dropped to normal and remained so until her death four days later. Four hours after the first injection of cortisone, eosinophiles had disappeared from the blood. Daily eosinophile counts and differential leucocyte counts on stained films were done but none of these cells were seen on subsequent days. The sternal puncture was repeated on the last day of treatment and the findings were identical with those already described. No changes due to treatment could be detected. The blood counts are shown in the chart. It is clear that the hæmoglobin levels and red cell counts dropped steadily despite treatment. It is of interest that "blast" cells appeared in the peripheral blood on the fifth day of observation and that terminally the leucocyte count rose to frank leukæmic levels. Twenty-four hours before her death the patient lapsed into a stuporous state. Petechiæ appeared over the front of the chest and abdomen and she died quietly on the sixteenth day of observation.



The post mortem findings were summarized as follows:

"Pathological diagnosis. — Myeloblastic leukæmia, with: (*a*) Myeloblastic metaplasia of vertebral and femoral bone marrow, of the spleen (270 grams), of the liver (1,980 grams) and of pulmonic lymph nodes. (*b*) Disseminated leukæmic infiltration of the kidneys, adrenal and thyroid glands, epicardium, endocardium, retroperitoneal tissues and pulmonary alveolar tissues.

"Associated conditions.—Cutaneous petechial hæmorrhages over the thorax and abdomen and subendocardial in the cardiac auricles; bilateral pulmonary œdema; atrophic endometrial polyp; visceral pallor; malnutrition; Minor aortic and coronary atherosclerosis.

"Comment.—In relation to the cortisone therapy we can detect no evidence of degeneration of any type in the leukæmic tissue which everywhere has an exceptionally well preserved cellular structure. Neither is there any evident alteration in the endocrine organs examined, namely thyroid, adrenals, pancreas and ovary, apart from leukæmic infiltrations seen in the adrenals and thyroid gland."

Permission to open the skull was not granted and it was consequently not possible to examine the pituitary gland.

SUMMARY

1. A case of acute leukæmia was treated with 2,100 mgm. of cortisone in doses of 100 mgm. 6 hourly by intramuscular injection.

2. The fever subsided and the patient stated that she felt "easier" but the disease progressed rapidly to a fatal termination despite this treatment.

3. There was no improvement in the blood picture and no alteration in the marrow findings.

4. Post mortem examination confirmed the clinical diagnosis. There was no evidence that the diseased tissue or endocrine glands had been altered by cortisone.

I am indebted to Drs. E. S. Mills and J. S. L. Browne for their help and advice, and to Dr. L. P. Chesney who referred the patient.

Cortisone was made available for the treatment of this patient through the courtesy of Messrs. Merck and Co. of Rahway, N.J., and the National Research Council of Canada.

In science address the few, in literature the many. In science, the few must dictate to the many; in literature, the many sooner or later, force their judgment on the few.—Edward Bulwer Lytton.

A REPORT OF 12 CASES OF TYPHOID FEVER TREATED WITH CHLOROMYCETIN

G. W. Wood, M.D., J. Alan Scott, M.D. and J. R. Bogert, M.D.

Magog, Que.

The twelve cases reported occurred in January and February, 1950. These patients all lived in the same locality or had been visiting in this locality, and had all obtained their water from the same well which was subsequently found to be infected. The families involved were all in the low income bracket and the hygiene practised was probably of a low order. The houses have inadequate plumbing and the privies used are on a higher level than the well. The outbreak occurred after a thaw of several days' duration when the land was covered with surface water. Four cases were females and 8 were males and ages ranged from 5 years to 49 years.

The symptoms were as follows: fever, 11 cases; headache, 10 cases; dizziness, 2 cases; vomiting, 2 cases; nausea, 1 case; chills, 1 case; diarrhœa, 1 case; chest pain, 1 case; sleepiness, 1 case aged 5 years. Temperature on admission varied from 101.4 to 104.8°, average 103.4°.

Diagnosis was confirmed in all cases by positive Widal tests and in 10 of the 12 cases stool culture gave the following results, there being no growth in 2 cases.

	Cases
S. typhosa O, S. typhosa H, S. Schottmuelleri O ..	7
S. typhosa O, S. Schottmuelleri H, S. Schottmuelleri O	1
S. typhosa O	1
S. typhosa O, B. abortus	1

The adults were started on daily doses of chloromycetin, 1.5 to 2.0 gm. in divided doses, and if a good drop in temperature had not occurred in two days the dose was increased. One 17-year old patient was started on 1.25 gm. and this was subsequently increased to 1.5 gm. In two adults the dose was increased from 1.5 to 2.0 gm., and in one to 2.175 gm.

The children were started on daily doses of from 0.5 to 1.5 gm. divided in a convenient manner. A 5-year old did well on 1.0 gm. and a 9-year old on 1.25 gm. A 6-year old and an 8-year old required 1.5 gm. Through a misunderstood order one 12-year old was given 0.25 gm. daily instead of four times a day, and this child did well but relapsed as is mentioned below.

Results.—There were no deaths, no complications, no abdominal pain, and no palpable spleens except in the case which relapsed, and in this case the child had to be readmitted to hospital ten days after discharge with abdominal pain, palpable spleen, and diarrhœa. This case was the one mentioned above who received the smallest dose of the drug. Normal temperature was achieved in the various cases from the third to the tenth day, the average being the sixth day. All cases were kept in hospital until two negative stools had been reported. One child was kept in hospital 33 days because his mother was in hospital and there was nobody to care for him at home. Other than this case, days in hospital varied from 17 to 26 days, the average being 21 days.

There was no reaction to the drug of any undesirable sort and patients taking the drug felt well and ate a full diet after temperature had returned to normal.

Relapsed case.—As was stated this case was readmitted to hospital 10 days after discharge with symptoms as stated and with a temperature of 103.6°. She was put on a dose of 1.5 gm. chloromycetin daily in divided doses. In 48 hours temperature had returned to normal, abdominal pain and diarrhœa had stopped. Ten days later she was again discharged with negative stool.

SUMMARY

Twelve cases of typhoid fever are reported. Chloromycetin is a very satisfactory drug for the treatment of typhoid fever. The dosage should probably be 2.0 to 2.5 gm. for adults and 1.0 to 1.5 gm. for children, these being daily totals and given in divided doses. In cases seen early hyperpyrexia and headache are the prominent symptoms. Therefore, patients who show unexplained fever and headache and who live in surroundings where typhoid fever might be expected, should have a Widal test done. Diarrhœa, vomiting, abdominal pain, and palpable spleen are only found in cases either seen late or inadequately treated.

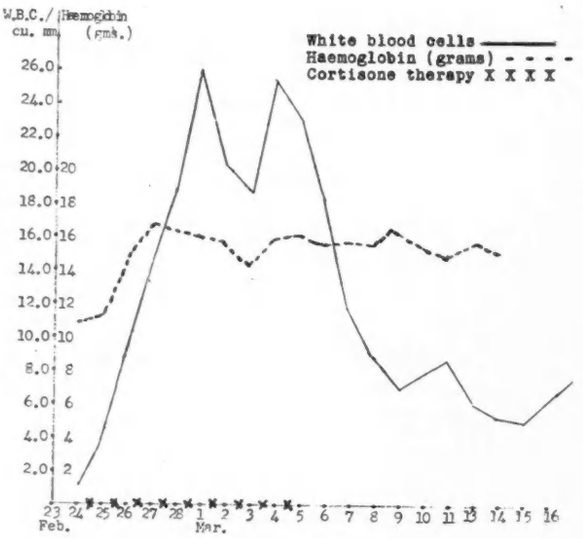
Treatment with chloromycetin is reported and dosage discussed. Growth from stool cultures is tabulated.

AGRANULOCYTOSIS TREATED WITH CORTISONE

A. L. Caldwell, M.D., J. W. Adams, M.D. J. F. C. Anderson, B.A., M.D. and A. A. Dick, M.D.

Saskatoon City Hospital, Saskatoon, Sask.

Until the present time the action of cortisone upon leucocytes has been primarily concerned with its reduction of eosinophiles and lymphocytes. With this end in view, the usefulness of the drug in cases of lymphatic and eosinophilic leukæmias is being assessed. In contrast, the potentiality of cortisone as a hæmatopoietic stimulant rather than as a depressant is suggested by the following case history:



The patient, a man aged 60, who had not been previously ill nor treated with sulfonamides, was admitted to the Saskatoon City Hospital on January 23, 1950, with acute appendicitis and a white blood count of 20,000. He underwent an emergency operation the same evening, at which a greatly enlarged, gangrenous appendix was removed and a considerable amount of thin, grey turbid fluid was aspirated from the abdomen. Postoperatively, catheterization by an orderly was required and when this was needed for the second time, the orderly was unable to perform it. Dr. J. M. Campbell, head of the Department or Urology, passed a catheter over a stilette and left it in on the evening of January 24. The patient was given two trulfazine tablets (each of which contained 2 3/5 grains each of sulfadiazine, sulfamethazine and sulfamerazine) t.i.d. on January 26, and this was reduced to one, four times a day, on January 27, continuing until the evening of February 7. As the patient was unable to void on every occasion on which the catheter was removed, a transurethral resection was performed by Dr. Campbell on February 8. Following this, he was given one trulfazine tablet, four times a day, from February 9 to February 19, when they were discontinued. On this day, his temperature had started to rise, reaching 103° at 4.00 p.m. It attained the same level on the 20th, at which time hæmatological investigations revealed: hæmoglobin, 66%; red blood cells, 3,500,000 and white blood cells, 975 with an absence of granular leucocytes. The patient was then given S.R. penicillin, 400,000 units per day, streptomycin, 1 gram b.i.d., pentnucleotide, 10 c.c. four times a day, liver extract, 2 c.c. daily and 500 c.c. of blood. On the following three days he was given 250 c.c. of blood per day.

On February 21, his temperature was 104.2° at 4.00 p.m., the 22nd 104.6° and the 23rd 105.4°. His clinical condition deteriorated, with signs of grave peripheral collapse with marked stupor on the morning of February 24. Sore throat had been present for one day. There was no mucous membrane ulceration, no bleeding or purpura, and the chest was clear. The blood pressure had fallen to 60/40 and he was unable to take fluids, previously taken well. At this time, he was seen in consultation by Dr. J. W. Scott, who advised the administration of cortisone.

On the evening of February 24, at 9.30 p.m., prior to the first dose of cortisone, the patient's condition was somewhat better. The temperature had dropped from 105.4 to 102.2°, his colour and respirations had improved and he was more coherent. At this point, 200 mgm. of cortisone was given intramuscularly in four depots of 50 mgm. each, followed by 200 mgm. the second day and subsequent dosages of 100 mgm. on the third, fourth and fifth days and 50 mgm. on the sixth, seventh, eighth and ninth days of its administration. The temperature dropped from 102.2°, just prior to the first dose of 200 mgm. of cortisone to a subnormal of 96.2° within fifteen hours with a corresponding fall in pulse rate from 120 to 76 and an appreciable rise in blood pressure to 100/60. The patient's clinical condition was very greatly improved on the morning following the first dose of cortisone and rapidly improved with blood pressure of 132/80 on February 26, pulse 64, mentally alert and able to take nourishment well.

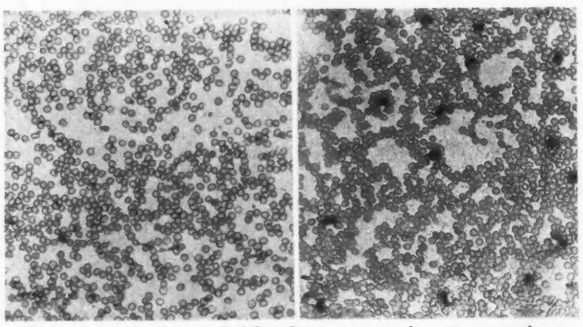


Fig. 1.—Peripheral blood smear prior to cortisone therapy. Wright's stain x220. **Fig. 2.**—Peripheral blood smear on the fifth day of cortisone therapy. Wright's stain x220.

COMMENT

In this case of profound agranulocytosis, the likely causative factor would appear to be the administration of small repeated doses of sulfonamide compounds in what is considered to be their least toxic combination. The standard therapeutic armamentarium of pentnucleotide, antibiotics, blood transfusions and liver extract was initially employed with evidence of early neutrophilic regeneration on the fourth day. With the substitution of cortisone, however, startling effects on the hæmatological findings were noted during the first few days. A resurgence of neutrophilic leucocytes into the peripheral blood mounted rapidly in ever-

increasing proportions. The total white count reached a peak level of 25,400 on the sixth day of treatment and 88% of the cells were of the granular leucocytic series. A preponderance of immature neutrophiles, at first, gradually subsided with about an equal proportion of mature and immature forms being reached on the fifth day. Further assessment of the pronounced transition from neutropenia to neutrophilia was gained by a study of sternal marrow obtained on the eighth day of cortisone therapy. Marked hyperplasia of the myelogenous elements was the striking feature with approximately 90% of the total nucleated count of 338,000 being in the granular leucocytic series.

Further significant though less striking observations included firstly an increased number of megakaryocytes in the sternal bone marrow. Secondly, a rise of the hæmoglobin level of the peripheral blood from 11 to 16 gm. % occurred during the first six days of cortisone administration.

To what extent the cortisone was responsible for the neutrophilia and increase in hæmoglobin and megakaryocytes also, is a matter of some interest. Dr. Scott's recommendation of the use of cortisone in this case was based on an observation which he had made in a case of rheumatic carditis treated with cortisone

TABLE I.

SERIAL DIFFERENTIAL COUNTS ON PERIPHERAL BLOOD

	Feb. 23	*24*	*25*	*26*	*27*	*28*	*Mar. 1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*13*	*14*	*15*	*16*	*17*
Segmented cells		3	18.5	19	29	46.0	47.5	42.7	42.0	34.0	40.5	45.5	47.5	51	40.0	46	40	35	35	55	37	46
Band cells		14	52.5	66	54	38.5	33.0	39.4	41.0	39.0	41.5	29.5	25.0	16	8.0	10	7	8	13	6	10	13
Metamyelocytes		2	5.0	2	4	3.5	6.0	5.7	5.5	5.0	3.5	2.0	0.5		1.0							
Myelocytes				6	3	3.0	2.5	4.7	4.5	3.5	2.0	3.0	2.0		0.5							
Eosinophiles																			1	1	1	2
Basophiles										0.5		1.0	2.0		4.5	4	7	6	3	1	2	2
Lymphocytes	91	57	18.0	5	8	6.0	7.0	5.0	4.0	13.5	9.0	14.5	21.5	29	40.5	30	41	46	47	35	46	35
Prolymphocytes	9	22																				
Monocytes		2	1.5	2	2	3.0	4.0	2.5	3.0	4.5	3.5	4.5	1.5	3	5.5	10	5	5	1	2	4	2
Disintegrated cells			4.5																			

↓ Cortisone Commenced ↓ Cortisone Discontinued

STERNAL PUNCTURE—MARCH 3rd, 1950

Total nucleated count: 338,800 per c.mm.

Differential:

Segmented cells	6.6%	Band cells	58.9%
Metamyelocytes	13.9%	Myelocytes	8.7%
Progranulocytes	2.6%	Lymphocytes	5.9%
Monocytes	0.8%	Eosinophiles	0.3%
Basophiles	0.1%	Metarubricytes	1.0%
Rubricytes	1.2%		

During the two weeks, following the cessation of cortisone, there was a gradual decline of the white blood count from the vicinity of 25,000 to 6,500 with a corresponding return of the differential count to normal proportions. No eosinophiles were observed in the peripheral blood at any time before or during the administration of cortisone. A small percentage of eosinophilic cells, however, was found in the sternal marrow. Occasional eosinophiles appeared in the peripheral blood on the ninth day following discontinuance of cortisone.

where there had been a neutrophilic rise corresponding with a fall in temperature. Dr. Scott thus reasoned that a similar effect might be expected in the case presented above, which happily was the result.

The usefulness of this drug, in cases of agranulocytosis, is indeed worthy of further investigation. Its possible therapeutic value in aplastic anæmia and thrombocytopenia may merit consideration. Time may well declare cortisone to be a powerful agent in the treatment of the above blood dyscrasias.

THE CANADIAN MEDICAL ASSOCIATION

Editorial Offices—3640 University Street, Montreal

(Information regarding contributions and advertising will be found on the second page following the reading material.)

EDITORIAL

THE GENERAL PRACTITIONER

SO much has been written on the place of the general practitioner and the future of general practice that another paper on the subject may not excite much attention. The report by Dr. Joseph H. Collings* on the present state of general practice in England today, is, however, not just another paper. No other comparable survey of general practice has been made; certainly none which is so outspoken. It deals with conditions of general practice in Great Britain, with a short reference to New Zealand, and in so far as it is critical of those conditions—and it goes very far—there is nothing for us in Canada to say. The author is well qualified to make such a survey, and while there are many respects in which his findings are debatable, the report as a whole must command respect for its obvious attempt to arrive at the truth.

But apart from his particular conclusions, Dr. Collings has managed to bring out aspects of the problems of general practice which are common to every civilized society. He feels that the present trend towards more and more hospital and specialist care must eventually cause the "elimination of general practice as an effective agency of medical care". To him, the general practitioner is the one remaining link "which gives the patient some continuity of care (and is) a focal point for dealing with the non-organic problems—the psychological, economic, and social worries of the people".

Who is to control this drift? The answer to that lies with no one section or body. Teaching bodies should contribute greatly. Organized medicine has a part to play. But eventually it is the general practitioner himself who must exert most influence and guidance. The formation of the Section of General Practice in our Association some two years ago was a forward step of the greatest value. This Section should produce constant discussion and examination of methods of attack on the whole problem of the changing aspects of general practice. It may be that the definition of a general practitioner needs overhauling. The older conception of his being one who undertakes everything cannot ever again be accepted. We would be willing to settle for his being one who always takes a general view of his patient, whilst exercising to the best of his ability whatever special training he may have. To speak of general practice being a specialty in itself is probably quite accurate, so far as it goes; but the word specialism bears the seeds of its own limitations. It is the good general practitioner who best deserves the oft quoted panegyric of Robert Louis Stevenson. It is he who must see to the protection of his high place.

* Collings, Jos. S., General Practice in England Today, *Lancet*, March 25, 555, 1950.

EDITORIAL COMMENTS

The Thiocarbazones in Tuberculosis

The American Trudeau Society has recently given a concise and up to date summary of the present status of drug therapy in tuberculosis.[1] We are suffering to some extent from excessive enthusiasm with regard to the treatment of tuberculosis, and the following sentence from the summary mentioned is a timely caution:

> "In many tuberculous conditions there is as yet no evidence that various drugs with anti-tuberculous properties lead to late results superior to those obtained by such established forms of therapy as bed rest and collapse therapy, although the use of the drugs appears to be associated with perhaps temporary favourable changes more promptly and more uniformly."

It is then pointed out that we do not yet understand the effects of these drugs on the immune forces of the host, nor their exact effect on tuberculous lesions. Add to these two large gaps in our knowledge that (*a*) these drugs have toxic effects, and (*b*) that drug-resistant strains of tubercle bacilli develop under their use; and it will be realized that we cannot yet depend on drug therapy as an alternative to the time-honoured methods of bed rest and collapse therapy, or other surgical procedures.

These cautionary remarks are all the more necessary because of the rapid production of new forms of drug therapy. Streptomycin with its dramatic immediate effects—too dramatic, unfortunately—is being supplemented with PAS in the hope both of greater effectiveness in the combination, and of delaying the development of bacillary resistance. There are

1. *Am. Rev. Tuberc.*, **61**: 436, 1950.

advantages in this combined therapy, but there are also limitations. Now, still another addition comes in the form of the thiosemicarbazones whose action is somewhat similar to that of PAS. So far, the work on this drug (referred to as TBl/698)* has been done almost entirely in Germany, and a report on its use in that country has been made by Hinshaw and McDermott.[2] These observers have advised further clinical investigation on this continent. The American Trudeau Society is encouraging these investigations, but emphasizes the point that the drug should not be employed generally in the treatment of tuberculosis until more is known of its limitations and potentialities. We entirely agree with that conclusion.

The Telephoning of Prescriptions

We have been asked to draw attention to the recent revision of food and drug regulations which clarifies the requirements for providing written prescriptions to pharmacists. It is pointed out by the Food and Drug Divisions that a telephoned order does not constitute a prescription. But a pharmacist may execute an order given over the telephone for emergency purposes, provided that such an order does not call for drugs on the schedule of the Opium and Narcotic Drug Act; and also provided that he is supplied with a written confirmatory prescription within 24 hours. Emergency telephone prescription has never been permissible for narcotic drugs.

It is also pointed out by the department that whilst a prescription is a definite order for a definite quantity of drug or drugs, it does not permit of refills unless the number of refillings is specified on the original prescription.

A pharmacist has a right to expect that telephoned prescriptions will be covered by written orders within 24 hours, just as any merchant selling goods on credit, relies on payment by the purchaser.

The work of the pharmacist can be considerably helped by co-operation of our profession in these respects.

Radioactive Compounds for Clinical Use

The Atomic Energy Control Board of the National Research Council has made arrangements for the distribution of radioactive compounds for clinical use. It is pointed out that only institutions whose facilities for handling radioactive isotopes have been approved by the Atomic Energy Control Board may use these compounds. Inquiries concerning requirements for approval should be directed to the Atomic Energy Control Board, Chalk River, Ontario.

It is to be anticipated that Canadian Institutions will take full advantage of the opportunity to use this peaceful application of atomic energy. Already much data have been accumulated on the treatment of thyrotoxicosis and carcinoma of the thyroid with radioactive iodine and polycythemia vera with radioactive phosphorus. Many fields in which these and other isotopes may be used for diagnosis and treatment remain to be explored and offer a fruitful field for investigation.

Inquiries concerning radioactive compounds for clinical use should be directed to Charles E. Frosst & Co., Montreal, who have been appointed distributors.

* It is known as "conteben" in Germany. It is available in Canada under the trade name of An-T-B (Nadeau Laboratoires, Montreal) and under various other names in the States.

2. *Ibid.*, January, 1950.

MEDICAL ECONOMICS

Medicine in Australia

[*The following comments on medical affairs in Australia are taken from a letter received by Dr. R. I. Harris of Toronto, who has been kind enough to send them to us. Dr. Harris' correspondent is a leading surgeon in Australia.*—EDITOR.]

It has been a great relief to us to see the present Socialistic Government go out. I do not say they are any worse or any better than the Government in England, but most of them were very ignorant men who became "power drunk" after nearly ten years in office. We were called "disgraces to humanity, vultures, moguls" and other abusive terms merely because we refused to co-operate with them on their terms. What a pity the doctors of England did not stand out as we stood out against the Government here. Furthermore, the doctors did not lose any opportunity of explaining to their patients their objections to Socialistic Medicine. Although I say it, I think we are a very good example of refusing to give in under stress, strain and abuse and on the whole, the public saw our point of view. We refused to be regimented and ruled; and if the public would have a free medical service then we should have some say in it. The government refused to consult on any details with the representatives of the profession. Fortunately, we have a constitution—unlike the United Kingdom—and the courts decided that they could not compel us to enter the service. I must say I was a bit surprised at the way the medical profession stood up in this matter and think it was largely the result of what went on in England; and our indignation at the disrespectful way the medical profession was

abused by ministers of the Government, *e.g.*, "practising on the poor at public hospitals" was one of the numerous insults.

In keeping with the awful class warfare that is a feature of life in this country at present, the Government sought to divide general practitioners from the specialists, thinking this was a simple class distinction that would split us: we specialists were specially selected for abuse. To give you an example of one of the things that was proposed, the highest fee a specialist was able to get was to be 25 guineas, but the general practitioners were to be paid a guinea (double fee) for night visits and so on; and operations that the Government thought general practitioners did, such as hernia and appendix, were high in proportion.

I had made up my mind that I would not join the service and risk the outcome. Fortunately, the Government went out. A large number of the Catholic clergy (I am a Catholic) took a very firm stand against them because they saw that all this regimentation was going to end in an authoritarian state with all its evils. In the State of Queensland, there has been Labour for twenty years but as a result of organized Catholic action, there was a terrific swing against Labour.

ASSOCIATION NOTES

THE ANNUAL MEETING

There is still time to make your reservation. Drop a note or use the application form to Dr. C. M. Jones, Halifax Infirmary, Halifax, Nova Scotia.

Since you are coming to Nova Scotia and are naturally interested in all matters pertaining to medicine, it seems fitting to tell you something of the background and activities of our profession in this Province.

Prior to 1868 there was no organized teaching of medicine in Nova Scotia. The apprenticeship system was in vogue, and after one or two years of it, the aspirant went elsewhere to spend two or more years and secure his degree. A number went to the United States schools on the Atlantic seaboard, notably Harvard, and others to the still older schools in England and Scotland. To teach adequately one must have hospitals, and the lack of them in Nova Scotia was the cause of our comparatively late beginning. True, there were two hospitals in Nova Scotia in 1757, one of them in Halifax, but it was a combination of hospital, poorhouse, and prison, and scarcely sufficient for instruction. However, in 1868, the Provincial and City Hospital opened in Halifax, and in the same year Dalhousie University organized its medical school. After five years of activity, the Halifax Medical College came into being, and carried on instruction in affiliation with Dalhousie until 1911, when it ceased to exist, and the whole activity was again restored to its original source.

Throughout the years the hospital facilities in connection with the medical school have enormously increased, and being centralized and adjacent to the medical school have constituted a source of instruction quite unique in character. Because of this, Dalhousie has been able to include a clinical fifth year in its course, and retain it when others less fortunate had to forego or abandon it. The aim is to turn out a well equipped general practitioner, the best basis on which to build. Dalhousie has an admission class of fifty-eight students in medicine, chosen from applicants who are bona fide residents of the four Maritime Provinces. It has been necessary to impose this restriction as to area, since this is the only school to care for the needs of a population of over one and one-half million.

In Nova Scotia there are two bodies dealing with the activities of medical practitioners. The first of these is the Provincial Medical Board, founded in 1872, which consists of thirteen physicians of whom seven are appointed by the Government and six by the Medical Society of Nova Scotia. Under the Medical Act the Board regulates the study and practice of medicine.

The second is the Medical Society of Nova Scotia, a branch of the Canadian Medical Association, which deals with the cultural, economic, and educational aspects of professional work. It is a voluntary organization, has an Annual Meeting which is a junior edition of that of the parent Association, and publishes a monthly scientific journal, the Bulletin. Under the auspices of the Society a voluntary prepayment health insurance plan was incorporated, Maritime Medical Care, Inc., which has already met with an excellent reception by the public.

Separate Branch Societies carry on individual work throughout the Province. The keynote of all efforts has been improvement of professional knowledge, standards and ideals.

In 1900 there were only three hospitals in Nova Scotia of a general type and in active operation. Today the Province is well served with institutions of all types. The Canadian Red Cross has established Outpost Hospitals in communities where the service was badly needed but the concentration of population scarcely warranted its initiation as a public enterprise. These have given excellent service.

The Victoria General Hospital in Halifax, is somewhat unique in that it is a large general hospital, owned and operated by the Govern-

ment of Nova Scotia. New construction has been under way for several years and when complete it will have a capacity of some 600 beds. It includes the central clinics for poliomyelitis, cancer, psychiatry, and neuro-surgery.

The medical profession in Nova Scotia is looking forward eagerly to this Annual Meeting of the Canadian Medical Association, and in every way will endeavour to do justice to the occasion.

H. L. SCAMMELL

The Annual meeting of the Society of Obstetricians and Gynæcologists of Canada will be held at The Pines, Digby, Nova Scotia, June 23 to 26 inclusive. Please make reservations through the Manager, at the above address.

APPLICATION FOR ACCOMMODATION
C.M.A. MEETING, HALIFAX, JUNE 19 TO 23, 1950

Dr. C. M. Jones,
Halifax Infirmary,
Halifax, Nova Scotia.

Please reserve the following:

(Indicate a first, second, and third choice).

Room(s) for ..... person(s) in .....

1. Hotel with private bath.
2. Hotel without private bath but running water in rooms.
3. Tourist Home — First Class accommodation.
4. Tourist Cabins, private bath. Outskirts of city. Bus transportation.
5. College Residences.
6. Private Home. Selected after inspection.

Will you notify committee if you cancel a reservation or secure accommodation with friends? .....

Any special request .....
.....
.....

Arriving Halifax ..... at ..... a.m.
(Date) (Hour) p.m.

Leaving .....

Means of Tranportation: Rail ..... Car ..... Plane .....

(NOTE: You will receive confirmation direct from the committee accepting the reservation when made.)

Are you willing to share a double room with another member of the Association? .....

Room(s) will be occupied by:

Name	Address	City	Province
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

(If children, please state age)

This application is submitted by me as:

(*a*) Member of Executive Committee.
(*b*) Delegate to General Council.
(*c*) Participant in Scientific Program.

Please send confirmation to:

Dr. .....
(Please print)

.....

.....

Canadian Society for the Study of Allergy

Canadian Society for the Study of Allergy Annual Meeting will be held in association with the Canadian Medical Association Meeting at Halifax, N.S., on Tuesday, June 20, 1950.

An interesting program has been arranged, including the following papers: (1) Dermatological Allergy; Dr. K. A. Baird, West Saint John, N.B. (2) Dandelion as a Cause of Hayfever; Dr. H. C. Jamieson, Edmonton, Alta. (3) Antibody Studies in Hay-fever in Children; Dr. Sidney Pedvis and Dr. Harry Bacal, Montreal, P.Q. (4) Some Clinical Problems in Allergy; Dr. I. H. Erb, Toronto, Ont. (5) The Use of ACTH and Cortisone in Diseases of Hypersensitivity; Dr. Bram Rose, Montreal, P.Q. (6) (Subject to be announced) Dr. C. R. K. Johnston, Department of Allergy, Cleveland Clinic, Cleveland, Ohio, U.S.A.

Canadian Ophthalmological Society

The thirteenth annual convention is to be held at "The Digby Pines", Digby, N. S., on Friday, June 23, and Saturday, June 24, 1950. For information, apply to: Dr. J. F. A. Johnston, Secretary, Canadian Ophthalmological Society, 174 St. George Street, Toronto, Ontario.

THE CAMSI COLUMN

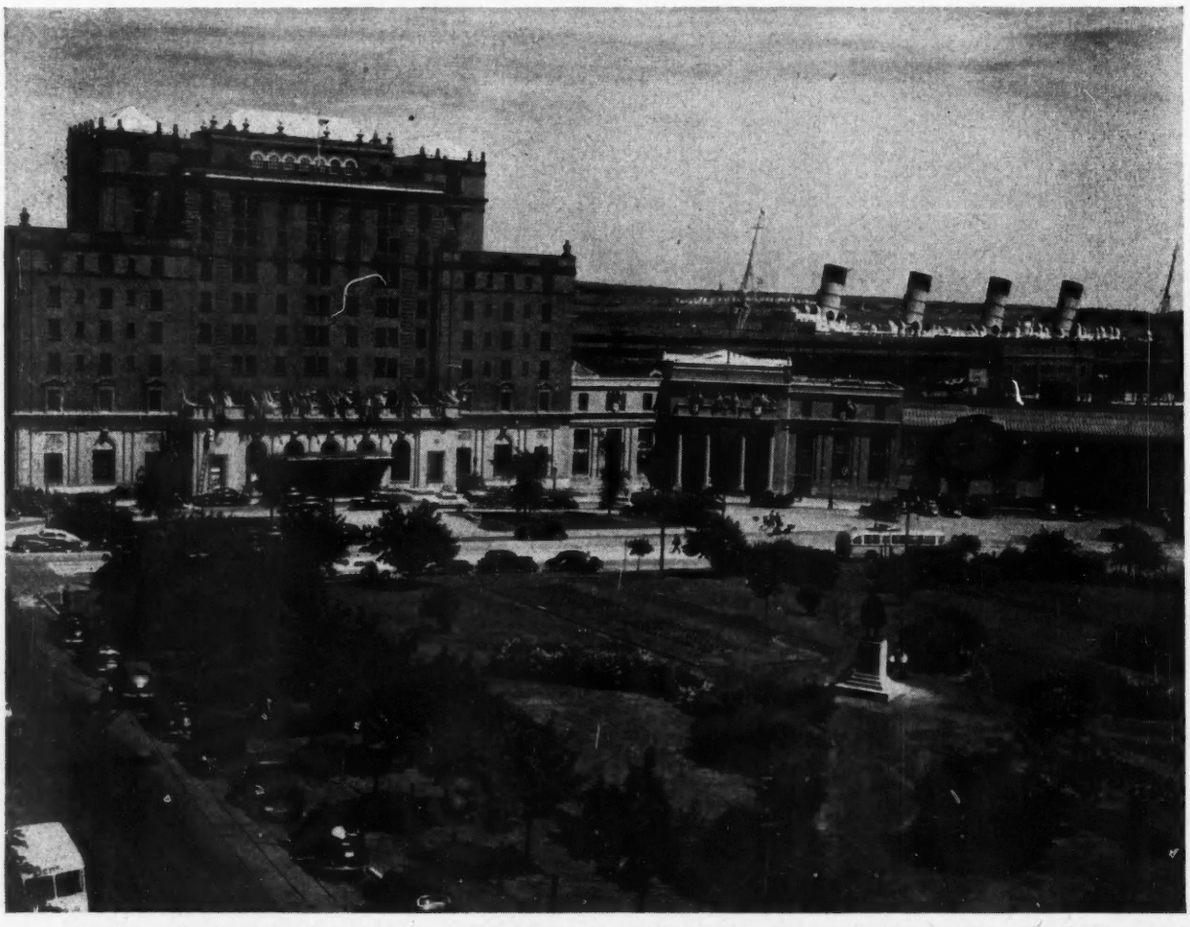
Doctors' Apprentices

Alert to the increasing incentive to specialize, CAMSI (The Canadian Association of Medical Students and Interns) has gone on record as favouring the principle of stimulating greater interest in the general practice of medicine.

It believes this to be a matter of education, more especially a broader and more intimate knowledge of the function, need, and value of the general practitioner in a community. Accordingly, a plan has been devised by which, through the active co-operation of practitioners in all parts of Canada, this education may be brought to medical students: doctors engaged in general practice are urged to accept a clinical year student as an apprentice during the coming summer months.

Write to the undersigned, giving name, address and special qualifications of the student if desired. This information will be presented to the students of Canada's medical schools, who will apply personally to such names received. Mr. Guy Lemieux, N.D.P.R., CAMSI National Executive, Room B'211, University of Montreal, 2900 Mount Royal Boulevard, Montreal 26, Que.

HEADQUARTERS OF THE ANNUAL MEETING AT HALIFAX, JUNE 19 TO 23, 1950



The Nova Scotian Hotel facing Cornwallis Square. Adjoining is Union Station, and in the background can be seen the "Aquitania", docked at the Ocean Terminals.

MEDICAL SOCIETIES

Winnipeg Medical Society

The Society has been fortunate this year in having distinguished British physicians and surgeons address its members. Sir Lionel Whitby gave the Gordon Bell Memorial Lecture in September. Sir John Parkinson and Sir Heneage Ogilvie spoke in November and December respectively. On February 24, Professor F. H. Bentley, Professor or Surgery, Durham University, Newcastle-on-Tyne, discussed recent research work on the gastric blood vessels illustrated by slides which showed direct communication between arteries and veins. Sir Reginald Watson-Jones at a crowded meeting in Theatre A, Broadway Bldg. of the University, lectured on March 2 on "Treatment of Common Fractures".

ROSS MITCHELL

Journée médicale en Mauricie

La Société médicale de Shawinigan et Grand'Mère organise pour le samedi 27 mai une grande journée médicale, à l'adresse de tous les médicins de la région du Saint-Maurice et des environs. Le programme, tel qu'établi à l'heure actuelle, comportera les activités suivantes: durant l'avant-midi, six conférences-éclair, par des conférenciers de la région, sur des sujets d'intérêt général. Cette séance sera suivie d'une discussion libre; à midi trente, buffet froid, à l'hôpital Sainte-Thérèse pour les médecins; à midi trente également, au Cascade Inn dîner-causerie pour les épouses des médecins; durant l'après-midi, symposium sur les maladies du foie et de la vésicule biliaire; par trois professeurs universitaires de Montréal; à 7 hrs p.m. souper-causerie avec comme conférencier un invité de marque. Les séances médicale auront lieu à l'hôpital Sainte-Thérèse de Shawinigan Falls. Les organisateurs s'attendent à la présence d'une centaine de médecins.

La société médicale des hôpitaux universitaires de Québec

Société médicale des hôpitaux universitaires de Québec vendredi, le 14 octobre, 1949.

Myasthenie grave chez un enfant de 4½ ans.—R. Thibodeau.

L'auteur rapporte un cas de myasthenie grave chez un enfant de 4½ ans. La maladie a débuté brusquement par une fatigue inexpliquée mais le premier signe révélateur fut la ptose des paupières. Quatre mois après le début de cette localisation, la pseudo-paralysie a continué son évolution pour envahir les muscles faciaux, les muscles des membres et ceux du tronc. La mort est survenue 6 mois après le début de la maladie, par défaillance cardiaque, au cours d'une crise myasthénique. Le traitement par la prostigmine et la radiothérapie du thymus n'ont pu enrayer l'évolution de la maladie. La thymectomie allait être tentée lorsque le malade est décédé. L'autopsie ayant mis en évidence une lésion thymique, on peut se demander, à la suite de certains auteurs, si ce malade n'entrait pas dans le groupe des myasthéniques qui auraient pu profiter de la thymectomie.

Pour faire suite à cette observation, l'auteur fait une étude de la myasthénie grave, insistant surtout sur les acquisitions diagnostiques et thérapeutiques récentes.

Glomerulosclérose intercapillaire (syndrome de Kimmelstiel et Wilson).—R. Lemieux, H. Nadeau et R. Lesage.

Le syndrome de Kimmelstiel et Wilson est un syndrome néphrotique s'accompagnant le plus souvent d'un syndrome d'artériosclérose et survenant chez les diabétiques. Il correspond à une sclérose marquée du tissu de soutien intercapillaire du glomérule de Malpighi. La lésion peut se présenter fréquemment sans le syndrome mais à des degrés moins avancés. L'apparition du syndrome chez un diabétique suffit à poser le diagnostic. Trois cas sont présentés dont le premier intéressant car on peut suivre chez lui l'évolution de la maladie.

Société médicale des hôpitaux universitaires de Québec vendredi, le 3 fevier, 1950.

Encéphalite non suppurée avec dissociation albumino-cytologique. — G. Desrochers, A. Pelletier et L. Bourgoin.

Observation d'une malade qui présentait un syndrome neurologique excessivement disparate, avec forte dissociation albumino-cytologique, témoignant d'une atteinte cérébrale vraisemblablement tumorale mais diffuse et sans signe de localisation; et un état mental ayant tous les caractères d'une démence authentique. L'évolution de la maladie au cours du séjour à l'hôpital, voire la régression des troubles neurologiques et biologiques, l'amélioration appréciable de l'état mental, nous ont fait porter le diagnostic de processus encéphalitique à virus probable.

Leucoencéphalite.—A. Pelletier et J. Delâge.

Les rapporteurs présentent le cas d'une patiente de 23 ans, qui, depuis deux ans, présente les troubles suivants: ralentissement global du psychisme, troubles de la mémoire, indifférence, myoclonies, crises convulsives épileptiformes, ataxie et troubles de l'équilibre. L'examen encéphalographique se lit comme suit: "Tracé très anormal correspondant à une encéphalopathie généralisée, comportant des accidents épileptiques et des décharges du type myoclonique. Ces constatations sont compatibles avec le diagnostic de leucoencéphalite" (Dr. C. A. Martin). Les rapporteurs concluent à un diagnostic de leucoencéphalite. Il n'y a pas de traitement connu de cette affection.

Rupture spontanée du cœur.—G.-H. LaRue et Y. Rouleau.

Un cas de rupture cardiaque chez un patient de 64 ans, située à la face antérieure du ventricule gauche, due à un infarctus récent du myocarde. L'évolution clinique se fit en deux temps, un intervalle de six heures entre la crise douloureuse et la mort. On signale la rareté de cette affection et le fait qu'elle est due à un infarctus récent.

Obésité post-encéphalopathique.—J. C. Miller et A. Blais.

Présentation d'un cas d'obésité extrême et monstrueuse, chez un garçon de 12 ans. Discussion du type de cette obésité, qui présente une répartition générale, sans prédilection spéciale pour aucune région particulière, et qui s'accompagne d'une croissance staturale également suractivitée: taille actuelle 66¼", poids 350 lvs. Aucune glande ne paraît prédominante au point de vue pathogénique; par contre à l'âge de 4 ans, accident nerveux central, à la suite d'indigestion aigue; inconscience d'environ soixante-douze heures, suivie d'hémiplégie droite transitoire, et ayant regressé en trois mois, pour faire place à une épilepsie convulsive également transitoire, et contrôlée définitivement vers l'âge de sept ans. Dès le début de ces accidents nerveux, l'embonpoint a commencé de se manifester sans jamais régresser. Si l'on rapproche ces accidents commateux associés aux manifestations épileptiques ayant à un certain moment libéré les centres d'encéphaliques du cortex cérébral, l'on peut présumer que les lésions ont touché l'hypothamus et les centres neurovégétatifs, ces derniers par voies endocrino-sympathiques sous-jacentes, régularisent normalement les fonctions métaboliques. Ce contrôle central semble ici suspendu ou perturbé, et la surcharge graisseuse reste inutilisée. Du côté psychique, arrêt de développement intellectuel et affectif, à l'âge approximatif des accidents initiaux et venant signer l'implication thalamique et corticale de ce syndrome encéphalopathique.

Société médicale des hôpitaux universitaires de Québec le vendredi, 4 novembre, 1949.

Presentation de classification d'interprétations radiologiques des pneumoconioses.—J. Gosselin.

Etude faite des différentes classifications déjà proposées et explications du mode de travail de la classification qui a présenté le plus d'avantages lors d'un travail d'interprétations radiologiques de dossiers de pneumoconioses.

Voici les divisions générales qui ont été utilisées: (*a*) aspect normal (négatif); (*b*) aspect réticulaire; (*c*) aspect micro-nodulaire; (*d*) aspect nodulaire; (*e*) aspect nodulaire et ombres diffuses; (*f*) ombres diffuses généralisées; (*g*) accentuation du dessin broncho-vasculaire; (*h*) tuberculose (cavernes).

Fistulisation bronchique d'un abcès pottique dorsal.—J.-P. Roger et M. Beaulieu.

Les auteurs présentent un malade souffrant d'une tuberculose vertébrale étendue à toute la colonne dorso-lombaire et compliquée d'un abcès ossifluent fistulisé dans la bronche souche gauche. Cette observation met en lumière deux faits principaux.

Tout d'abord, il est souvent difficile de faire le diagnostic d'un mal de Pott à forme diffuse superficielle. Les lésions vertébrales sont très discrètes et seules les couches osseuses sous-périostées participent au processus inflammatoire. Ce n'est souvent qu'à l'occasion de la prise d'une radiographie démontrant l'existence d'un abcès en fuseau ou simplement un élargissement des masses paravertébrales qu'on peut localiser un foyer pottique. La constatation de nombreux becs de corbeau ou de ponts ostéophytiques réunissant les corps vertébraux peut prêter à confusion et en imposer pour un rhumatisme vertébral surtout en l'absence de complications nerveuses ou de fistules.

Enfin la fistulisation d'un abcès pottique dans les voies respiratoires constitue une complication grave contre laquelle le chirurgien est pratiquement désarmé. Toutefois, depuis l'apparition de la streptomycine, il semble qu'on puisse espérer la guérison dans certains cas.

Dilatations bronchiques des lobes superieurs. — R. Desmeules, F.R.C.P.[C.].

L'auteur rapporte cinq observations qui sont une nouvelle preuve de la fréquente étiologie tuberculeuse des bronchiectasies des lobes supérieurs. Le diagnostic de dilatations bronchiques est suspecté avant l'introduction du lipiodol mais il faut reconnaître que la bronchographie lipiodolée est le procédé qui permet d'établir le diagnostic de certitude. Les antibiotiques peuvent être utilisés lorsque l'infection bronchique présente des signes d'évolution aiguë ou subaiguë.

L'auteur hésite à croire que la lobectomie puisse trouver une indication fréquente chez des malades qui souffrent peu de leurs ectasies bronchiques et qui ont le plus souvent une histoire ancienne ou actuelle d'infection tuberculeuse.

CANADIAN ARMED FORCES

News of the Medical Services

Group Captain A. A. G. Corbet, Director of Health Services, R.C.A.F., assumed the chairmanship of the Inter-Service Medical Committee on April 1, 1950, relieving Surgeon Captain A. McCallum, R.C.N., Medical Director General, R.C.N. The chairmanship of this committee which is responsible for the co-ordination of the medical services of the armed forces, is held for one year in rotation by the medical directors of the Navy, Army and Air Force. The Director General of Dental Services and a representative from Defence Research Board are *ex-officio* members on the committee.

The United States Atomic Energy Commission is sponsoring a series of short courses in the treatment of radiological casualties with a view to training a nucleus of Service and civilian doctors who upon return to their units or practices will be able to disseminate the information among their colleagues. The following medical officers from the Armed Forces and Department of Veterans' Affairs attended the first course which commenced March 27, 1950, in the universities indicated. Wing Commander J. A. Sifton, R.C.A.F., University of Chicago. Surgeon Lieut.-Commander J. W. Fleming, R.C.N., University of Rochester. Major C. C. H. Leavens, R.C.A.M.C., Johns Hopkins University. Dr. Jules Gosselin, D.V.A., University of Rochester.

Dr. J. S. Fitzsimons, a graduate of Dublin University, 1946, was recently commissioned as Surgeon Lieutenant, R.C.N., and appointed for duty in R.C.N. Hospital, Halifax, N.S. Prior to entry in the R.C.N., Dr. Fitzsimons was Medical Officer of Health, Department of Public Health and Welfare, Newfoundland.

Flight Lieutenant L. A. Wright of the Institute of Aviation Medicine visited England, representing the R.C.A.F. in development of mutual equipment. While there, he spent a period of time at the R.A.F. Institute of Aviation Medicine, Farnsborough, Hants.

A. McCALLUM

CORRESPONDENCE

Psychogenic Factor in Asthma

To the Editor:

Dr. H. K. Detweiler's paper on the psychogenic factor in asthma appearing in the February number of the Journal recalls to mind a case which illustrated the influence of this factor in initiating an attack: The patient was a 50-year old man with a history of asthma for years for which he was taking adrenaline almost daily. Six days before his wife was to enter hospital for a surgical operation, he developed a very severe attack which was so prolonged that the wife's plans had to be changed.

Personality evaluation showed this man to be very conscientious, meticulous and perfectionistic. He had not taken a holiday in about twenty years. Although he hated mistakes he was never able to reprimand his subordinates. He was sensitive to the opinion of others, avoided arguments and tended to take other people's troubles on himself. Marriage did not occur until age forty and then only after a lengthy engagement. He appeared to be still very attached to the memory of his parents. Both, especially the mother, were spoken of with great admiration although they had been very strict people. The wife was spoken of in precisely the same terms and with the same feeling that were used in connection with the mother.

The threatened separation from the wife seems to have been the emotional factor precipitating this severe attack. This agrees with the conclusion of French that asthmatic attacks tend to be precipitated by situations that threaten to separate the patient from some mother figure. Probably the long postponement of marriage was due to over-attachment to the mother. Finally, having taken a wife as mother figure he never related to her as a husband, but continued his old pattern of emotional relationship to the mother. He was constantly striving to gain approval from everyone by his perfectionism, and at the same time inhibiting his aggression which he "took out on himself". Unfortunately, there was no opportunity to go into the relationship between previous attacks and emotional conflicts, but there seems little doubt that in the attack described, the fear of separation from the wife was the determining emotional cause.

F. W. HANLEY

Regina General Hospital,
Regina, Sask., March 17, 1950.

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

The Cost of the N.H.S.

The old childhood adage about being healthy, wealthy and wise has taken on a new and sinister implication as a result of the publication of supplementary estimates including the huge additional sum of £98,730,000 for the National Health Service. This brings the net cost of the Service for 1949-50 up to the staggering figure of £419,100,000, of which £363,200,000 is borne by taxation. The total cost for 1948-49 was £302,000,000. This is by no means the end of the story, as the Government's forecast for 1950-51 is £450,000,000.

These figures have been assailed on two main grounds: that the discrepancy between the original estimates and the final outlay indicates either carelessness or lack of supervision of spending, and that the country cannot afford to spend this tremendous sum on a health service. As *The Times* has expressed it in a leading article: "it is intolerable that Parliament should still be asked to supply scores of millions of pounds for purposes no better defined than 'maintenance and running costs' of the hospitals, 'including specialist services', and with no more evidence that the money is to be well spent on necessary objects than the assurance of one Minister in one speech". A careful study of the official report of the debate in the House of Commons on the subject gives no indication that either the Chancellor of the Exchequer or the Minister of Health has appreciated the seriousness of the situation.

Some Striking Figures

Analysis of the figures now made available reveals some interesting facts and contrasts. The average family doctor's net income during 1949-50 was £1,530, compared with £2,300 for the average dentist. In this connection it is not amiss to note that the original estimate for family doctors was practically the only item that did not require to be increased by an appreciable amount. The estimates for chemists' bills was hopelessly out, having to be increased by three-quarters, and the final figure shows that the average family doctor is spending about £1,770 a year on prescriptions. This works out at 14s. 8d a head of the population, compared with 9s. 10d. a head in 1948-49. The cost of the ophthalmic service has been practically doubled, the original estimate for the year being £14,700,000 and the final figure £25,100,000, and it is estimated that about 7,000,000 people must have visited ophthalmologists or opticians during the year.

To measure health in terms of pounds, shillings and pence may be wellnigh impossible, but it is becoming increasingly evident that the nation is paying a heavy price for the unseemly haste with which the National Health Service was introduced. How the flood of expenditure can be slowed down without penalizing the population is a problem for which there is no easy solution. It will require powers of statesmanship of which at the moment, unfortunately, there are no signs.

A Critique of General Practice

By a curious coincidence, the full consequences of which have yet to be seen, it was while the nation was recovering from the shock of realizing for the first time the full price of the National Health Service, that *The Lancet* published a reconnaissance of "General Practice in England Today" by Dr. Joseph S. Collings, "a young Australian who had previously studied medical work in his own country, in New Zealand, in Canada, and in the United States". Dr. Collings, who is at present research fellow, Harvard School of Public Health, Boston, Mass., was given a grant by the Nuffield Trustees to study general practice in this country. The report is one of the most outspoken documents that has ever been published in a medical journal. Of the validity of many of the criticisms there is no question, but in the limelight of publicity which has inevitably been focussed upon it the sense of proportion and balance which is necessary to assess its true significance has been lost. The lay press has seized upon it with an avidity which may well have unfortunate consequences. Even Dr. Collings, with all his efforts to be scrupulously fair, has not been able to avoid the pitfall of laying undue emphasis upon the defects of general practitioners. To analyze carefully such a complex affair as general practice is a task which is probably beyond the wit of any one man. One of the obvious fallacies in Dr. Collings' thesis is that he has entirely ignored the fact that general practice in this country is traditionally an art and not a science, and the mere fact that every patient is not submitted to full laboratory investigation does not necessarily mean that the patient is being neglected. We may be considered old-fashioned in the "Old Country", but we still look upon our patients as "persons" and not "cases".

That much requires attention goes without saying, and it is hoped that once the sensational aspects of this Report have been allowed to find their true level, action will be taken to remedy some of the faults to which attention has been drawn, not only by Dr. Collings, but also by general practitioners themselves, *e.g.*, the two articles by a rural and an urban general practitioner in the review of the Service published by *The Practitioner* last autumn: "The National Health Service Act in Great Britain". Outstanding among these is the urgent need for provision of health centres, and a careful and critical review of what are to be the functions of the general practitioner in the new Service. Is he to be reduced to the status of a glorified clerk, or is he to be allowed to retain some of the functions of the old family doctor, such as the care of the pregnant mother, the children in his practice and the opportunity to follow his patients through hospital?

WILLIAM A. R. THOMSON

London, April, 1950.

ABSTRACTS FROM CURRENT LITERATURE

Medicine

Functional Systolic Murmurs in Children. Messeloff, M. D.: *Am. J. M. Sc.*, **217**: 71, 1949.

Recent studies have shown that from 8 to 20% of school children present systolic murmurs that are thought to be functional. This represents a large number of children whose cardiovascular system must be studied in order to rule out organic disease. The differentiation is often difficult and about 25% of all children examined by the cardiac consultation service are classified as possible heart disease, most commonly on the basis of a systolic murmur whose significance could not be definitely evaluated. The sole cardiac abnormality in the 300 children observed in this study was a systolic murmur. To avoid confusion in describing cardiac murmurs, the author applies the term "functional murmur" only to individuals in whom structural valvular changes can be reasonably excluded and who are free of any disease, general or cardiac, that is known to cause a systolic murmur.

Employing a standard form and nomenclature, the murmurs were described and analyzed. The analysis showed that functional murmurs do not possess a pathognomonic feature that can distinguish them from organic murmurs and that various characteristics are common to both types. Thus, in both, some transmission of murmurs is found and in neither can the site of maximum intensity or the effect of position or exercise on the presence or intensity of the murmur be used as conclusive evidence in the diagnosis. Nevertheless the present study showed that functional murmurs are always systolic in time, are always faint or moderate in intensity and in over 90% of cases are musical or blowing in quality and are of short duration. However, while organic murmurs are characteristically loud and long, some of them are faint and short.

In individual cases, the characteristic features may not be diagnostic and a complete examination, not only a cardiovascular examination, is necessary to properly evaluate the systolic murmur. All technical aids in the investigation of cardiac disease should be utilized. Only by careful interpretation and correlation of all collected data can one establish a correct diagnosis of a functional murmur in a high percentage of cases. When the functional character of the murmur has been established, the physical activities of the child should not be restricted. To do so leads to suspicion and may initiate or perpetuate a cardiac neurosis. J. F. SIMPSON

Vitamin E in the Treatment of Angina Pectoris. Ravin, I. S. and Katz, K. H.: *New England J. Med.*, **240:** 331, 1949.

A small, carefully selected group of eleven patients with angina pectoris were treated with daily doses of 500 mgm. of vitamin E (approximately 250 mgm. of alpha tocopherol) for periods varying from four to twenty-four weeks. A two-step exercise tolerance test, carried out under rigidly controlled conditions, was employed as a measurement of objective improvement. Slight subjective improvement occurred in two cases. Slight objective improvement was possible in one patient. NORMAN S. SKINNER

Gastrojejunocolic Fistula. Faxon, H. H. and Schoch, W. G.: *New England J. Med.*, **240:** 81, 1949.

The results of treatment in nine cases of gastrojejunocolic fistula are presented. The condition is a late and serious, if uncommon, sequela of gastroenterostomy. It arises through the perforation of a marginal ulcer into the colon. The clinical course is usually rapidly downward, diarrhœa and marked loss of weight resulting from reflux of irritating large bowel content back into the stomach. The reverse flow of gastric content into the bowel is largely prevented by the folds of the jejunum.

The treatment of gastrojejunocolic fistula consists of the surgical removal of the fistulous tract with restoration of bowel continuity. Where the general condition of the patient is not satisfactory preliminary ascending colostomy markedly lessens the operative risk. Because of the frequency of subsequent development of peptic ulcer in these cases vagotomy is recommended to overcome the ulcer diathesis and this is best done by the transthoracic approach after the patient has fully recovered from the repair of the fistula. Treatment of the ulcer diathesis by gastric resection at the time of repair of the fistula is hazardous surgery because of the presence of adhesions and the danger of peritonitis. NORMAN S. SKINNER

Arachnidism. Greer, W. E. R.: *New England J. Med.*, **240:** 5, 1949.

Arachnidism, the syndrome arising from the bite of the black-widow spider, has been reported from all but seven of the United States. This type of spider is considered to be increasing in numbers and is invading the large cities, being found in greatest numbers in the vicinity of human habitations. The importance of recognition of arachnidism lies in the fact that it may be mistaken for an acute abdominal condition and lead to unnecessary operation. Transient excruciating pain at the site of the bite is rapidly followed by local redness, œdema and a burning sensation. The latter passes over the entire body and passes off after 20 to 30 minutes. Sudden abdominal pain, often cramp-like in nature, occurs and there is associated weakness, restlessness and an extreme fear reaction or even hysteria. Headache, nausea, vomiting, cramps in the arms and legs and burning of the soles of the feet may be complained of. This later symptom is probably pathognomonic. Shock may be profound, with marked lowering of blood pressure and a moderate leukocytosis.

Of the many therapeutic agents employed in the treatment of arachnidism the most efficacious is considered to be the intravenous administration of calcium gluconate. Successful treatment of six cases with this agent is reported. NORMAN S. SKINNER

Aureomycin in the Treatment of Primary Atypical Pneumonia. Finland, M., Collins, H. S. and Wells, E. B.: *New England J. Med.*, **240:** 241, 1949.

Twenty cases of primary atypical pneumonia, selected because they were not apparently in a stage of spontaneous recovery, were treated with aureomycin by mouth. The dosage employed was one gm. every four to six hours until the temperature was substantially normal for two to three hours, then one gm. every six to eight hours for two to three days. Fever and symptoms subsided promptly in all cases within twelve to forty-eight hours (in the majority within twenty-four hours). Cold agglutinins were demonstrated in the sera of all patients late in the course of the disease or during convalescence. The rapid recovery in all cases in this series indicates that aureomycin possesses a specific and marked value as a therapeutic agent in primary atypical pneumonia. NORMAN S. SKINNER

Acute Focal Œdema of the Brain in Children with Head Injuries. Pickles, W.: *New England J. Med.*, **240:** 92, 1949.

Head injury in children may give symptoms identical with those of subdural hæmorrhage except for rapid and complete recovery within a relatively short time. Such a picture is considered to be due to acute focal œdema of the brain. Eight such cases are presented, all making a complete recovery. In one case operated upon for suspected subdural hæmorrhage cerebral œdema was evident. NORMAN S. SKINNER

Nitrate Methæmoglobinæmia. Marcus, H. and Joffe, J. R.: *New England J. Med.*, **240:** 598, 1949.

Methæmoglobinæmia may follow the ingestion of nitrates in well water (which is being reported with increasing frequency) or in medicinal agents. A case of methæmoglobinæmia following the use of bismuth subnitrate in an infant with diarrhœa is reported. The nitrates are changed to nitrites within the bowel by bacterial action and nitrite absorption is more apt to occur with a diseased bowel. The diagnosis is made clinically by the presence of a grayish-brown cyanosis and a chocolate-brown colour of the blood. Chemical analysis of the blood will demonstrate nitrites and the diagnosis may be proved by the use of the spectroscope or spectrograph. Within the body nitrites oxidate the ferrous ion to the ferric form and hæmoglobin is changed to methæmoglobin. The use of bismuth subnitrate as a therapeutic agent is unnecessary, unwarranted and hazardous. It should be replaced by bismuth subcarbonate in the physician's armamentarium. NORMAN S. SKINNER

Surgery

Gastro-intestinal Gas. Maddock, W. G., Bell, J. L. and Tremaine, M. D.: *Ann. Surg.*, **130:** 512, 1949.

Observations were made on a series of patients during anæsthesia, operations and pyelography. Swallowed air is the main source of gastro-intestinal gas and is encountered mostly in nervous patients and especially in those who relax the superior œsophageal sphincter, either voluntarily (as do habitual belchers) or unconsciously. If the superior œsophageal sphincter is relaxed and an attempt made to breath against the closed glottis 1,000 to 2,000 c.c. of air can be drawn into the œsophagus in 3 to 5 minutes. When the patient is lying down this gas may pass on down the gastro-intestinal tract, but if he is conscious and erect it is belched or eructated. It was found that during the early stages of anæsthesia varying quantities of air may be swallowed, especially during ether induction. Very large quantities of air may enter the stomach during anæsthesia with curare and cyclopropane and positive pressure artificial respiration if the inferior pharyngeal sphincter is relaxed.

A case is reported in which a patient having a tooth root removed under pentothal aspirated so much air into her stomach that it perforated and an enormous pneumoperitoneum developed. At operation a rent 4.5

cm. in length near the cardia was closed. This gastrointestinal air passes along the tract very much more rapidly than food does: in from 30 to 120 minutes it passes as flatus in normal subjects. The phenomenon of meteorism in pyelography was found to be explicable on the same basis. Continuous gastric suction will prevent meteorism during cystoscopy and pyelography as well as postoperative distension. Under many conditions patients become "temporary aerophagics".

BURNS PLEWES

Obstetrics and Gynæcology

The Obstetric Capacity of the Undilated Cervix. Fitzgerald, T. B.: *J. Obst. & Gynæc. Brit. Emp.*, **56:** 229, 1949.

The cervix has been shown to be a predominantly fibrous structure. In its upper part, at the internal histological os, there is a sharply demarcated zone, where the tissues become predominantly smooth muscle. This anatomical structure is correlated with the behaviour of the cervix during labour. The vaginal cervix has normally little part in restraining precipitate progress of the presenting part. The muscular zone in the supravaginal cervix acts as a sphincter which physiologically controls the speed of advance of the presenting part. The indications for immediate delivery being present, it is the state of this region which must be the criterion of "deliverability". The degree of dilatation of the external os may be gravely misleading when used as an indication of the practicability of immediate vaginal delivery.

P. J. KEARNS

A Case of Transplacental Metastasis of Malignant Melonoma from Mother to Fetus. Holland, Sir E.: *J. Obst. & Gynæc. Brit. Emp.*, **56:** 529, 1949.

A case is described of a young woman with a primary malignant melanoma in the skin of the thigh; local removal was followed by recurrence. A second more extensive operation was followed by marriage and pregnancy; during pregnancy recurrent growth became disseminated throughout the body. Delivery near term was effected by Cæsarean section, with the patient apparently in a dying state and a large mass (the placenta) in the lower uterine segment. The child was alive and well, and the mother recovered from operation and died 3 months later. The placenta was found to be massively infiltrated with melanotic growth of the same type as that in the skin; melanotic tumour cells were found in a blood-vessel of a chorionic villus. The child died at age of 10 months with its liver enlarged by 4 nodules of a melanotic growth similar to that in the mother's skin and the placenta. Transmission of the malignant growth from mother to fetus via the placenta is considered proved. References to related types of case are given.

P. J. KEARNS

Chemotherapy in the Treatment of Malignant Disease. Cade, S.: *Brit. M. J.*, **2:** 1193, 1949.

There is little doubt that the late stages of cancer of the breast can be influenced by sex hormones. Although mostly favourable, these hormones do at times cause aggravation of the disease. The mode of action of the hormones is not understood, and this today is the most urgent problem. Hormones, like castration, produce their effect on the host and thus differ from all other methods of treatment of cancer which aim at a direct attack on the tumour. Hormones have thus opened up completely new avenues, and at present they are more important as research weapons than as therapeutic agents.

ROSS MITCHELL

Pruritus Vulvæ. Jeffcoate, T. N. A.: *Brit. M. J.*, **2:** 1196, 1949.

Pruritus seems to be a very particular type of response, and it is almost specific to certain forms of stimuli or to stimuli arising under special circumstances. The state of central nervous system is probably important, especially if fatigue of the higher centres is present.

The secret of the successful treatment of pruritus vulvæ lies in determining the cause. Discharges rarely make the vulva itch unless the infecting organism is either *Trichomonas vaginalis* or one of the fungus group, usually *Oïdium albicans*. Trichomonas infection is the leading cause of pruritus vulvæ, especially in the childbearing period. It was found in 100 cases in a series of 254 consecutive cases (pregnant women excluded). Glycosuria occurred in eight cases. If there is any doubt about the cause of pruritus the only safe procedure is a glucose-tolerance test. In glycosuria without diabetes the pruritus is nearly always the result of *Oïdium albicans* infection, which thrives in the presence of a free supply of carbohydrate. In general, mental and emotional upsets should be accepted as causing pruritus vulvæ only when every other possibility has been excluded. Prolapse seems to be rare but none the less definite cause of pruritus. Allergy and drug sensitivity may occasionally cause pruritus. Senile vaginitis, possibly associated with vulval atrophy is occasionally associated with pruritus. Various deficiency states; *e.g.*, avitaminosis of A and B complex, anæmia and achlorhydria can cause pruritus and can be shown to be responsible for approximately 20% of cases of the series. The most important part of the management of pruritus vulvæ is a thorough investigation to find the cause. A definite organic cause amenable to treatment can be found in four out of every five women who complain of pruritus vulvæ and in not more than 5% is it impossible to give real relief.

ROSS MITCHELL

Observations on Human Leucocytes During the Menstrual Cycle. MacKinnon, I. L.: *J. Obst. & Gynæc. Brit. Emp.*, **56:** 404, 1949.

Total and differential leucocyte counts of 7 healthy young women were investigated on 201 occasions over a period of 6 months. Results for the combined group of females prove that there is an increase in the number of total leucocytes, neutrophil cells, lymphocytes and monocytes during the follicular and luteal phases of the menstrual cycle followed by an abrupt decrease during the bleeding phase, the changes being more marked in the case of the neutrophil cells than in the case of the lymphocytes and monocytes. Graphs of the numbers of leucocytes during the menstrual cycle are shown to be closely related to the level of blood-œstrin and to body temperature. It is suggested that the numerical changes in the leucocytes during the menstrual cycle are under ovarian control. Periodographic analysis applied by Schuster's method to 150 counts in 2 females failed to reveal a definite periodicity in the number of monocytes in the individual females.

P. J. KEARNS

Tuberculous Ulceration of the Vulva: With report of one case successfully treated with streptomycin. Mathew, A. G.: *J. Obst. & Gynæc. Brit. Emp.*, **56:** 408, 1949.

The frequency, etiology, clinical features, pathology and treatment of tuberculous ulceration of the vulva have been discussed. A case of tuberculous ulceration of the vulva, associated with tuberculosis of the urinary tract, is described. The tuberculous ulceration of the vulva was healed by treatment with streptomycin.

P. J. KEARNS

Pregnancy and Adnexal Cysts. Haas, R. L.: *Am. J. Obst. & Gynec.*, **58:** 283, 1949.

The coexistence of adnexal cysts and pregnancy occurred with a frequency of one in each 304 pregnancies. Complications of these cysts, such as torsion, rupture, hæmorrhage or suppuration did not occur. Obstruction of the birth canal occurred only once and was readily overcome. Nine of the cysts were functional while ten were neoplastic. Teratomas, including dermoids, accounted for five cysts. Ovariotomy during early pregnancy does carry some risk of producing an abortion.

Operations carried out in the second trimester involve practically no risk of abortion. A plan for the management of cysts discovered during pregnancy is presented.
ROSS MITCHELL

Psychiatry

An Introductory Outline of a Short Method of Psychotherapy. Gottschalk, L. A.: *J. Nerv. & Ment. Dis.*, **110:** 315, 1949.

This is a summary of much literature on psychotherapy, and the summary itself cannot be summarized further, but it is worth drawing attention to it for busy physicians who could get guidance for the psychotherapeutic handling of their patients by reading the entire article. The author of the paper has told the abstracter that he now considers the article somewhat naïve from the viewpoint of his later further training in psychotherapy. This might serve to introduce the point that skill in psychotherapy requires not only clinical experience, as stressed by the author, but also a dynamic understanding by the doctor of the inter-relationships between his feelings and those of the patient. Even though it gives little emphasis to this aspect, the paper has considerable merit, since the need for some kind of psychotherapy is so widespread it seems better for physicians to acquire some kind of "rules" for psychotherapy instead of waiting until psychiatric education has accomplished sufficient spreading of a more subjectively sophisticated approach.
W. DONALD ROSS

Significance of Maternal Bereavement Before Age of Eight in Psychiatric Patients. Barry, H.: *Arch. Neurol. & Psychiat.*, **62:** 630, 1949.

The histories of 1,683 psychotic patients have been reviewed for the age of the patient when the mother or father died. The incidence of the loss of the mother was found to have been greater before the age of 8 than would be expected in comparison with the incidence of loss of the father. Deaths of parents after the patient was 8 were comparable between the parents in accordance with the usual male and female death rates. The loss of a mother before the age of 8 appears to be one of the many factors with which the development of a psychosis is associated. A study of 330 psychoneurotic patients indicated some trend in the same direction. This report emphasizes the importance for mental health of the maintenance of maternal care during at least 8 years of childhood.
W. DONALD ROSS

Pathology

Pathologic Changes After Partial Hepatectomy: With Special Reference to Hepatic Necrosis in Protein-Depleted Rats. Gurd, F. N. and Vars, H. M.: *Arch. Path.*, **48:** 140, 1949.

The authors report the results of a 70 to 77% partial hepatectomy in 230 rats following an adequate diet and a 14 day period of protein depletion. Changes in the remaining liver tissue are discussed primarily; analytic and metabolic data have been reported elsewhere. Following an adequate diet partial hepatectomy was well tolerated. In protein-depleted animals partial hepatectomy resulted, however, in massive necrosis of the remaining liver in a small number of rats. There was failure of the usual regeneration of liver tissue and mitotic activity was conspicuously absent. It is suggested that survival of the animal is dependent on a prompt regenerative response, which was absent in the protein-depleted animals.
GEORGE F. MEISSNER

Pathogenesis of Experimental Hepatic Fibrosis and Cirrhosis in the Dog. Gillman, T. and Chaikoff, I. L.: *Arch. Path.*, **48:** 67, 1949.

This paper is a presentation of a comparative study of several forms of hepatic fibrosis and cirrhosis produced in dogs by various experimental means, and reported singly in previous papers. Three pathologically distinct forms of hepatic fibrosis have been produced in dogs. Briefly, these are peri-hepatic vein fibrosis, periportal fibrosis and diffuse interstitial fibrosis. The association of fibrosis with intracellular fatty change is more obvious in the first form, although sometimes present in the other two. While the early stages of these three forms are clearly distinct, the final pathological picture may be similar and confusing. This is due to distortion of the liver lobule and to occasional mixtures of two or more types. The authors point out that the variable presence or absence of fatty change indicates that other factors than hepato-cellular degeneration should also be considered responsible for hepatic fibrosis. In this regard they draw attention to the possible part that circulatory changes might play. They were able to demonstrate no correlation between a particular type of hepatic fibrosis and the experimental procedure used to induce it.
CHAS. W. JONES

Incidence of Fatal Coronary Disease in Non-diabetic and in Diabetic Persons. Clawson, B. J. and Bell, E. T.: *Arch. Path.*, **48:** 105, 1949.

50,775 postmortem records are statistically analyzed with regard to fatal coronary disease in non-diabetic and diabetic subjects. There were 1,182 diabetic patients. The results are tabulated with regard to sex and age distribution. It is shown that fatal coronary disease is about twice as frequent in diabetic males and three times as frequent in diabetic females as compared with non-diabetic subjects. The widely held impression, that diabetes accelerates coronary arteriosclerosis, is thus confirmed by statistical analysis of a large autopsy material. It is further pointed out that this accelerating effect is more pronounced in female patients.
GEORGE F. MEISSNER

Pædiatrics

Revascularization of the Brain. Beck, C. S., McKhann, C. F. and Belnap, W. D.: *J. Pediat.*, September, 1949.

The authors report on a new neurosurgical method of increasing cerebral blood flow by means of an artificial arterio-venous fistula between the common carotid and the internal jugular. This was undertaken in view of Penfield's findings in post-traumatic and post-anoxic brain scars, in which live neurones were found imprisoned among glial cells and very poorly supplied with capillaries. The fistula, aiming to arterialize the veins of the brain, is established on the right side and is completed by ligation of the vein proximal to the fistula. The operation has caused no pulsating exophthalmos, and but a temporary elevation of the cerebrospinal fluid pressure. Eleven patients have been operated on, 4 of whom, including 3 children, are reported. These are a 19-month-old retarded child; a 4-year-old child showing retardation and convulsions and having a history of neonatal cyanosis; and an 11-month-old child suffering from repeated convulsions since a possible meningitis at the age of 2 months. All of these patients showed appreciable improvement, particularly regarding convulsions.
PAUL DE BELLEFEUILLE

Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood. Sabin, A. B. and Feldman, H. A.: *J. Pediat.*, **35:** 296, 1949.

Report on the recent developments in the diagnosis of infantile toxoplasmosis, particularly concerned with two new serologic tests, the specific significance of which would appear to be greater than that of the tests previously used and reported on by Sabin. One of the tests described is a complement-fixation reaction using an antigen prepared from an allantoic culture of *Toxoplasma*. The other is based upon an altered affinity for methylene blue exhibited by the organism when it has been mixed with antibody. Both these tests are positive at very high titres (1:1,000 to 1:4,000) in recently infected animals and remain so for long periods. The authors insist that the diagnosis of infantile toxo-

plasmosis is not justified without serological evidence in both child and mother. On the other hand, they recall that the skin test can be negative in persons having evidence of circulating antibody. It is always negative in well children from 0 to 5 years, but it is positive in at least 65% of middle-aged people who show no sign of disease. The same is true of low titres of serum antibodies. Concerning the relation of chorioretinitis in infants to toxoplasmosis, it has been found that among the children showing this eye lesion, 90% of those having positive serology also have intracranial calcifications demonstrable by x-ray, whereas these exist in only 5% of the patients with negative serology. Apart from the proved cases of toxoplasmosis, similar chorioretinal lesions have been described in cases of retrolental fibroplasia, of congenital cataracts due to rubeola in the mother, in other cases of multiple malformations of the brain and eyes, and in what appears to be a new syndrome consisting of multiple vascular degeneration with hyaline thickening of the vessel walls, retinal atrophy and cerebral softening. PAUL DE BELLEFEUILLE

Industrial Medicine

Chronic Disease as an Industrial Hygiene Problem. Selby, C.: *Am. J. Pub. Health,* **39:** 598, 1949.

In this article which is one given at a symposium on chronic disease, the author reports briefly on the use of vital statistics in industrial health administration and practice, by citing experience of the General Motors Corporation, Detroit, Michigan, to which he is medical consultant. The modern industrial health maintenance program is organized to furnish the following services: (1) Diagnosis and treatment of all occupational injuries or illnesses. (2) Temporary care of minor non-occupational ailments and First Aid in non-occupational emergencies. (3) Consultations for necessary medical advice. (4) Assistance in the diagnosis and control of tuberculosis and other communicable diseases. (5) Examination at the time of employment to aid in proper placement on a job for which the employee is best suited. (6) Periodic examinations to aid in the maintenance of the employee's health. (7) Granting of sick leaves and approval of return to work. (8) Plant inspection and control of possible sources of occupational diseases.

The author shows how these services can vary from year to year. In the Corporation referred to, the medical department engineers a new industrial health model each year; specifications are based on the previous year's experience and trends, as shown by vital statistical studies. The author illustrates the precedure by referring to their chronic non-occupational sickness experience during the calendar year 1947. Tables are included to show the non-occupational disability rates for both male and female employees, and the non-occupational death-rates. It is seen that diseases of the organs of movement—chronic rheumatism, myalgia, arthritis and neuritis—were the most important source of chronic disability among males. These are not causes of death but they lead to impairment and disability. Diseases of the nervous system were prevalent among women. In both sexes, diseases of the heart, blood vessels and kidneys gave high rates. Based on these findings, the present industrial health maintenance program is planned to give particular attention to rheumatism and diseases of the nervous and vascular systems. Examinations, consultations and health education give special attention to these ailments. MARGARET H. WILTON

The Importance of Keeping Medical Information Confidential. Fourcher, K. R.: *Med. Bull.,* Standard Oil Company, etc., **9:** 64, 1949.

For many years the Standard Oil Company (N.J.) has held the following policy: All medical diagnoses and other confidential medical information are kept within professional channels unless there are legal obligations (industrial accidents or public health regulations) or it is to the advantage of the patient to disclose them, which is done only with his permission. In this article the author who is the medical doctor of that company discusses the importance of this policy and shows how it works in the best interests of both the employee and the company.

He indicates its relation with each contact which the worker may have with the medical department—pre-placement examination, periodic examination and, special examination for reasons of age, illness or retirement. In reporting results of pre-placement examinations, management can be given information it needs to properly place the person, without details of physical or temperamental disorders. In this way medical information remains confidential.

When physical defects are found on periodic examination, the doctor should present the facts so clearly that the worker will take the necessary corrective measures. Sometimes an employee may be undertaking, or, may wish to undertake, duties which exceed his physical capabilities. Reassignment of duties or refusal of promotion is necessary. At such time the rôle of the doctor is very important. He must act in the best interest of the patient without releasing confidential details. In cases of retention or retirement, no medical details that led the doctor to his conclusion should be released. Excerpts are given from statements regarding the opinions and practices of several other large companies. In all these, the standing of the medical division was such that their recommendations could be accepted as the basis of official action. In these firms, management comes into the picture only when its services are needed. The author states, however, that many of the smaller companies have not yet had enough experience to realize how important it is to retain medical information as confidential. This has been recognized only by some of the large progressive companies which have long had medical departments.

MARGARET H. WILTON

OBITUARIES

Dr. Sidney B. Biehn died at his home in Mimico on Monday, January 16. He was in his 79th year and for some time had been in poor health. Dr. Biehn was born at Bright, in Oxford County and graduated from the University of Toronto in 1895. He practised at Elmwood and Kitchener prior to coming to Parry Sound in 1906. Here he remained for forty years where he had a large practice and enjoyed the confidence and respect of his many patients. For some years he was Medical Officer of Health for the town and Chief Coroner for the District of Parry Sound. In politics he was a lifelong Liberal and took an active part in campaigns in the interests of his party. He is survived by his widow, three sons and one daughter.

Dr. Andrew L. Campbell, aged 65, of Kitchener, Ont., died at St. Mary's Hospital March 15 after a brief illness. A graduate of the University of Western Ontario, he had practised medicine in Kitchener for more than 25 years, coming here from Edmonton where he practised for 10 years. Born near Belmont, Ont., Oct. 7, 1884, he spent his early youth there before entering university. Dr. Campbell was a member of Grand River Lodge, A.F. & A.M. and also of the Knights Templar and Shrine at Edmonton. Besides his widow, he is survived by one son, one daughter, three brothers and one sister.

Dr. Walter William Chipman, distinguished Montreal physician, died at his residence in Montreal after a brief illness. He was 84. Born in Wolfville, N.S., he was educated at Acadia University and later went to Edinburgh University where he obtained his M.B. in 1895 and his M.D. in 1898. He did postgraduate work in London, Paris, Vienna and Berlin. For a time he was resident physician at the Edinburgh Royal Infirmary,

the Royal Maternity Hospital and Bolton Infirmary. He returned to Canada and in 1900 was appointed demonstrator in gynæcology at McGill and a member of the staff of Royal Victoria Hospital. In 1910 he was named professor of gynæcology and in 1912 he became professor and head of the new department of obstetrics and gynæcology. In 1929 he resigned from active teaching at the university but remained until quite recently closely connected with the faculty of medicine through his services as a member of the Board of Governors of McGill and of the Royal Victoria. He was named a governor of the hospital and a member of the executive committee in 1933 and was president from 1943 to 1947, helping to guide the hospital through the difficult war years. He became a member of the board of governors of the university in 1932 and retired in 1948.

He was an honorary fellow of the Royal College of Obstetricians and Gynæcologists, which he helped to establish 30 years ago, and was also a Fellow, a past president and past governor of the American College of Surgeons. Dr. Chipman was also a Fellow of the Royal College of Surgeons, Edinburgh, and held honorary degrees of doctor of law from the University of Pittsburgh, Acadia University, and the University of Bishop's College. He was governor of the American College of Surgeons from 1938 to 1941 and was president in 1925. He was predeceased by his wife. There were no children.

Dr. Cyril James, Principal and Vice-Chancellor of McGill University, said of him.

"Dr. Chipman came to McGill more than half a century ago. As a teacher, a physician and more recently as a member of the board of governors he strove unceasingly to aid its progress and raise it closer to the splendor of his own ideals. These facts were recorded in a resolution presented to him by his colleagues when he resigned from the board in December, 1947.

"McGill can never forget the contributions that he has made but during the tomorrows when we have but the memory of his personality to bear us company we shall recall most frequently the wise and understanding heart of a great man who was our friend."

AN APPRECIATION

The passing of Dr. Walter W. Chipman removes from our midst a colourful figure who was closely associated with tradition of the old school. Yet, until the very day of his departure he was keenly interested in the modern trends of university and hospital activities. First and foremost he was a doctor who combined in true proportion the art and science of medicine. Other outstanding characteristics were numerous and varied but particular mention is made of his capabilities as administrator, teacher and orator. Perhaps his most remarkable accomplishments were made possible by means of his ability to interest and open the door of opportunity for young medical men in the constant struggle to progress in the scientific world.

An astute clinician and skilful surgeon he was admired and beloved by his patients, students and hospital staff. It has been aptly said that Dr. Chipman brought to his medical career not only great professional ability but the spirit that makes medicine a true human ministration. He will go down in Canada's medical history as one of those who knew well that to be a great surgeon one must also be in spirit a great gentleman.

We mourn his loss but we are happy in the memories of our close association with a leader who was firm but fair, debonair in manner and one who possessed great professional ability.

N. W. PHILPOTT

Dr. Hugh Daniel Chisholm died at his home in Springville, Pictou County, Nova Scotia, March 12, in his 67th year. He was born at Springville, attended Pictou Academy, and graduated from Dalhousie University in Medicine in 1907. Following graduation he practiced for a short time at Wabana, Newfoundland, but soon returned to his native village. For over forty-years he conducted a rural practice in a large territory where he was the only physician. He was greatly beloved by the people to whom he was friend and counsellor as well as doctor.

Dr. William Alexander Coghlin, aged 72, of Trail, B.C., died in the Trail-Tadanac Hospital on March 28. Dr. Coghlin graduated from Manitoba in 1907. He practiced for three years at Grenfell, Saskatchewan, and joined a classmate, the late Dr. J. Bain Thom, at Trail in 1910, where he practised continuously until ten days before his death. While in the army during the First World War he became interested in radiology and continued in this specialty for the rest of his life. A hard worker, his integrity and strict adherence to what he believed was right gained for him the respect and confidence of all members of the community in which he lived.

He belonged to that group of men who, by hard and conscientious work, have served Canada well and have gained for the medical profession the honoured position it holds today. The lives of such men could be studied with profit by the younger members of the profession.

M. R. BASTED

Dr. James A. Cummins, aged 86, who had practised medicine at Bond Head, Ont. nearly all his life, was instantly killed on March 10 and his wife critically hurt when they were struck by a car as they stood beneath a bulbless light standard just inside the village.

Dr. Bernard Francis died at his home in Sydney Mines on April 2, after a long period of ill health. He graduated from McGill University Medical School in 1899, and his entire professional life was spent in Cape Breton.

Dr Joseph Gagnon, décédé le 2 mars, à l'hôpital Général d'Ottawa, à l'âge de 65 ans, après une courte maladie. Né à St-Basile, le 3 août 1885. It fit ses études au séminaire de Joliette, puis à l'Université Laval de Montréal. Le Dr Gagnon était établi à Buckingham depuis 1911; depuis 25 ans, il était attaché à l'hôpital St-Michel comme anesthésiste. Le défunt était Chevalier de Colomb du 4e degré, ancien président de la ligue du Sacré-Cœur, membre de l'Union St-Joseph.

Il laisse dans le deuil trois frères et une sœur.

Dr. James Richard Gilroy, died at his home in Oxford, N.S., March 30, at the age of 74. He was born at Saltsprings, Cumberland County, and was a member of the teaching profession before entering upon the study of Medicine at McGill University. He graduated in 1904 and in the autumn of the same year began to practice in Oxford continuing to do so until forced to retire due to ill health in November, 1949. He took an active part in the life of the community and served it in many positions of trust and importance.

Dr. Karl Gottleib died suddenly on March 8 in Montreal in his 57th year. A native of Austria, he studied in the University of Vienna, graduating in medicine in 1920. He practised in Vienna, being specially interested in children's diseases, and worked there with the world-famous children's specialist, Professor Tandler. He made Canada his home 10 years ago, practising in Montreal. Surviving him are his wife and a brother.

Dr. Gordon Hyland, aged 63, died March 4 at the Toronto General Hospital. Dr. Hyland was born in Toronto. He attended Upper Canada College and graduated in medicine from the University of Toronto in 1909. During the First World War he served with the rank of major in the 10th Field Ambulance Corps. After the war he was a captain in the Royal Grenadiers. Dr. Hyland practised medicine for several years in Toronto. Throughout the Second World War he was prominent in Red Cross work and member of the Toronto branch executive for several years. He served as chairman of the speakers' committee and was made president in 1947. He also rendered valuable service as vice-chairman of blood donor services for Toronto. He was made an

honorary life member of both the Canadian Red Cross and the St. John Ambulance Brigade.

An enthusiastic golfer, he was a member of Rosedale, York Downs and Eastbourne golf clubs. He was also a member of Grace Church-on-the-Hill and the Royal Canadian Yacht Club. He leaves his widow, one daughter, a granddaughter, his mother and one brother.

Dr. Edwin Alfred Jones died at his home in Winnipeg on March 23, after a long illness. Born 77 years ago at Balsam, Ont., he was educated there and at Whitby. In 1899 he graduated in medicine from the University of Toronto and did postgraduate work in England. In 1905 he came to Winnipeg and practised continuously. He served for a time on the honorary attending staff of the Winnipeg General Hospital and was especially interested in pædiatrics. His sports were golf and curling and he was a member of Niakwa Golf Club and of Meridian Lodge No. 140 A.F. & A.M. He served in the official board of Crescent Fort Rouge United Church of which he was a member. He is survived by his widow, two sons Dr. E. A. and G. M. Jones and three grandchildren.

Dr. W. O. MacDonald died suddenly at his home in Saint John, March 12. He was 52 years old. He received both his B.A. and M.A. from St. Joseph's University and his M.D.C.M. from McGill. Dr. McDonald served as a physician on the staff of the Saint John General Hospital from his intern days to the time of his death. He was chief in medicine at the General and had been president of the Medical Board of St. Joseph's Hospital. He was a Fellow of the American College of Physicians and certified in Diabetics by the American College and in Medicine by the Royal College of Canada. In the reserve army Dr. MacDonald served with No. 14 Field Ambulance, and in the second World War he rose to the rank of Lieut.-Col. in the R.C.A.M.C. As an additional service during the recent war he was field secretary for the N.B. Division of the Medical Procurement and Assignment Board. His brief in this capacity was outstanding. He also was active in planning for the proper provision of blood services to the armed forces. Dr. MacDonald was a devoted Catholic and was active in many community services, church and lay.

He was gifted with a fertile imagination and possessed a driving energy which carried his plans to completion. His practice as an internist was specially concerned with diabetes and hæmatology. As a young man "Ossie" MacDonald was an athlete specializing as a runner and baseball player. His friends were many of all races and creeds. In his busy life he did much for his profession, his church and the community.

Dr. Leo McCabe, died on Feb. 16 at his home in Windsor, Ont., in his 63rd year. He graduated in medicine from the University of Toronto in 1908. Beside his widow, he is survived by two daughters, two sons, two brothers and a sister.

Dr. John Archibald Marquis, aged 75, died at his home in Brantford. Ont., March 23. Dr. Marquis was born in Mount Pleasant in 1875. Receiving his early education in Brantford public school and collegiate, he graduated from University of Toronto in 1896, becoming associated with his father. The practice now is being carried on by Dr. J. A. D. Marquis, son of John and grandson of Duncan. For half a century Dr. J. A. Marquis was physician for the Ontario School for the Blind and the Widows' home here. He leaves his widow, two daughters and a son.

Dr. William Henry Mulligan, aged 85, died at his home in Sudbury, on Feb. 28, after a short illness. Surviving are his widow, a brother, five daughters and a son.

Dr. R. McG. Nichol died at his residence in Cornwall on March 22. Born in Listowel, Ont., 78 years ago last January 20, he secured his B.A. at the University of Toronto in 1894 and his medical degree in 1897. He came to Cornwall in 1899 and had practised his profession here and in this district since that time. He served as a member of the board of trustees of Cornwall High School, now the C.C.V.S. He also served the ratepayers in the town council for one term. He was a member of Cornwall Lodge No. 125, A.F. & A.M., of Karnak Temple of the Mystic Shrine and of St. John's Presbyterian Church, Cornwall. He is survived by his widow, a daughter and a son.

Dr. Frederick George Pim died on March 9 following a heart attack. He had returned from Toronto earlier and had made one or two calls on foot due to storm and returned to his home where he collapsed at the breakfast table. Dr. Pim was a native of Toronto and graduated from the University of Toronto faculty of medicine, in 1934. He started practicing in Keswick on Lake Simcoe. When war broke out in 1939, he joined the staff of General Motors at Oshawa where he was engaged in industrial medicine for two years.

Later he went to British Guiana as medical officer at a mining settlement 65 miles up the Demarara river where bauxite is mined and shipped to Canada for the making of aluminum. He returned to Canada in July, 1946. He is survived by his widow, a son, one daughter and two sisters.

Dr. John Clarence Webster, M.D.C.M., C.M.G., D.Sc., LL.D., F.R.C.P., FA.C.S., F.R.S., died at his home in Shediac, N.B., March 16, aged 86 years. Dr. Webster's health had been delicate for some years, but his mental activity never flagged, and his keen interest in affairs and particularly in the history of Canada was a constant spur to physical effort sometimes surprising in a man of his age. He is survived by his widow and a son, Dr. Wm. L. Webster, a research physicist.

Dr. Webster was chairman of the National Historic Sites and Monuments board for the last seven years. He has done more for the preservation of Historic Sites in the Maritimes and perhaps in all Canada than any other man. He was continually assisted by his distinguished wife. Fort Beausejour Museum and the New Brunswick Museum and the restoration of forts at Louisburg, N.S. are largely the result of personal work and influence of Dr. Webster. His contributions, many at his own expense, are a permanent contribution to the history and art of Canada. His collection of Wolfe documents, maps and portraits is the most complete in the world. The later life of Dr. Webster in history and letters is so well known that his connection with medicine is apt to be forgotten. However, it is as a physician that we are doubly proud of this great man. His early education in Shediac followed by an arts degree from Mount Allison University prepared him for his medical education in Europe. He was gold medallist at Edinburgh in 1891, then studied in Leipsig and Berlin. He was assistant professor of obstetrics and gynæcology at Edinburgh. A lecturer in gynæcology at McGill, and a staff member of the Royal Victoria Hospital. For twenty years he was chief of the departments of obstetrics and gynæcology at the University of Chicago and at the Chicago Presbyterian Hospital. He was known, too, as an aviation enthusiast. When the late General Italo Balbo of Italy led a squadron of Italian flying boats around the world in 1933, the squadron landed in front of Dr. Webster's house at Shediac. He was donor of the Webster Trophy, awarded annually to the amateur pilot who contributes most to Canadian aviation during the year. The trophy was given in memory of Dr. Webster's son Capt. John C. Webster, killed in a flying accident near Montreal 19 years ago.

The list of his honours from universities and governments and learned societies is a remarkable one. His interest and influence were always felt in any community in which he lived. His ideas did not always win immediate public acclaim, but they were generally right. He was beloved as well as respected by all who met him and he had a great love for youth of all ages, in other words he had a rare feeling for persons younger than

himself and was able to sense their interests and associate himself with their ambitions and problems. He was outspoken in favour of free enterprise, thrift and self-reliance.

His epitaph must be written by many for he was many things to many people and the facets of his mind reflected the impact of any idea presented to his notice.

A. S. KIRKLAND

Dr. George Hudson Wilson, died in South Burnaby on February 11.

NEWS ITEMS

Alberta

The following medical men of Edmonton have returned from a postgraduate course in Chicago; Dr. W. W. Eadie; Dr. H. A. Lloyd; Dr. C. R. Dobson and Dr. J. R. Kelly.

Dr. Victor Wright has been appointed as Director of the Diagnostic Cancer Clinic for the Government of Alberta. Dr. Wright holds the position previously held by Dr. E. L. Pope whose passing occurred at the close of the last year. Dr. R. C. Riley is the Associate Director with headquarters in Calgary. A third diagnostic Clinic is being formed in the city of Lethbridge.

The Workman's Compensation Board of Alberta is commencing its new building in the central part of the City of Edmonton. It will be a large and imposing structure on one of the "future" great thoroughfares of the city.

The Edmonton Academy of Medicine held its monthly meeting in the Medical building, April 5. Dr. H. A. Lloyd presented a paper upon "Acute and Sub-acute Thyroiditis" while Dr. S. B. Thorson of Calgary spoke on "Some Common Patterns of Headaches". The meeting was well attended.

Dr. J. P. Johnson of Edmonton has recovered from his recent illness and is again attending to his practice, we welcome Dr. Johnston back to the "active files". Dr. T. H. Field is convalescing satisfactorily following a short hospitalization period.

Dr. John D. Duffin of Calgary has opened a general medical laboratory in the Medical Arts Building. This new and much needed laboratory will cover the present day tests used in medical practice, especially, biochemistry, metabolic and functional tests and hæmatology.

Dr. D. G. Revell, Emeritus professor of Anatomy of the University of Alberta keeps ever busy in numerous worthwhile hobbies and attends most of the scientific meetings held at the University.

W. CARLETON WHITESIDE

British Columbia

Following a practice which has been carried on for the past two or three years, the Medical Staff of the Vancouver General Hospital had as its Guest Chief of Staff Dr. Cecil J. Watson, of the Medical Department of the University of Minnesota. His visit was during the week March 27 to March 31, inclusive. His time was very fully occupied with clinics, ward rounds and lectures, and his visit was a very great success.

Dr. Myron M. Weaver, Dean of the Medical Faculty of the University of British Columbia, is a very busy man these days, organizing his staff for the opening of the Medical Faculty next September, when the first class will be admitted. We understand that the number admitted will be about seventy, chosen from a very large list of applicants.

As might be expected, the affairs of the British Columbia Hospital Insurance Commission occupied a large part of the deliberations of the recent session of the B.C. Legislature, which has just come to a close. There was a great deal of comment from the opposition, as was natural, but unfavourable comment was by no means confined to them. A good many of the members, who were loyal Coalitionists, expressed themselves in no uncertain terms, and at least partly as a result of their stand in the matter, a motion designed to give the Cabinet a completely free hand in the matter of setting the amount of dues to be paid, had to be amended by the setting of a maximum figure of $36.00, beyond which the dues cannot be raised without further recourse to the Legislature as a whole. No very clear facts seem to have emerged otherwise, but the whole scheme is at present under very close scrutiny, with a view to affecting economies and greater efficiency of operation.

The B.C. Division, Canadian Cancer Society has launched its annual "Conquer Cancer" Campaign for funds—its objective this year being $100,000. Last year it collected $150,000 in this way, and this money has been put to excellent use already. Especial emphasis is being laid on research, and in accordance with this, a sum of $50,000 was granted to the B.C. Research Institute, which is now partly in operation, under the supervision of Denis Lock, technician. Only temporary quarters are as yet available, but permanent offices and laboratories are contemplated for the near future. Other grants make it possible for doctors, nurses and physicists to take advanced training at great world cancer centres; the education of the public is strongly emphasized; and a fund has been set up to provide "housekeeping services" where these are urgently necessary. Up to date, some 210 patients have benefited from this fund.

Chief Constable Walter Mulligan of Vancouver began some time ago to organize a "disaster plan" for Vancouver and its surrounding area. This is gradually taking shape, and has received the hearty sympathy and support of the Vancouver City Council; the Mayor, Charles Thompson having agreed to serve as chairman of the Plan Committee. Air Marshal F. V. Heakes will be chief co-ordinator. Sub-committees will be appointed, headed by the chiefs of the Fire Department, City Engineer's Department, Health Department, representatives of the Red Cross, and so on. The Plan will be co-ordinated with Canada's Civil Defence organization, through liaison with General F. F. Worthington.

The twenty-fifth annual meeting of the Canadian Tuberculosis Association will be held in Vancouver from May 15 to May 20, of this year. More than 400 are expected to attend this meeting, including many of the continent's most eminent chest surgeons and specialists in tuberculosis. Secretaries from every provincial Tuberculosis Association will be present, as well as representatives from the Trudeau Society of the United States.

The West Coast General Hospital of Port Alberni will observe Hospital Day on May 14, with Miss K. Bailey, the Superintendent of Nursing, in charge. A special effort is being made by the hospital auxiliary to build up an adequate library for the use of the new hospital, and a large number of books have already been received.

The current Red Cross campaign for funds in British Columbia has already realized half its objective, which was set at $500,000 for this year. Several branches have reached or passed their quota already. Weather conditions in the interior, where the severe winter has left roads in an almost impassable state, have hampered some of the workers, and it may be some time before the work here can be completed.

J. H. MACDERMOT

Manitoba

Dr. Bram Rose, Assistant Professor of Medicine, McGill University, delivered the first Tisdall Memorial Lecture in the Medical College, Winnipeg, on March 10. His subject was ACTH and Hypersensitivity. It was much appreciated.

Dr. Jessie McGeachy spoke on "Psychosomatic Considerations of Some Gynæcological Problems" before the Section of Obstetrics and Gynæcology of the Winnipeg Medical Society on March 6.

Professor Frappier of Montreal addressed a group of doctors and others on B.C.G. The meeting took place in the Central Tuberculosis Clinic on March 15.

The Princess Elizabeth Hospital owned and operated by the City of Winnipeg was opened on March 23. It is located close to the other municipal hospitals, the King Edward for tuberculosis and the King George for infectious diseases. The new hospital contains 120 beds and is intended for the care of patients who are convalescent or who suffer from chronic diseases. It will relieve other hospitals in the city which minister to acute cases, and will enable sufferers from chronic ailments to be studied and properly treated.

The Western Canadian Section of the Canadian Anæsthetists Society met in Winnipeg, March 23 and 24. Thirty-six registered, including 15 visitors, one of whom was Dr. Rod Gordon, Toronto, secretary of the Canadian Society. The guest speaker was Dr. LeRoy Van Dam of the University of Pennsylvania. Dr. Van Dam addressed a meeting of the Winnipeg Medical Society on March 24, his subject being "The Anæsthetic Management of the Obstetrical Patient". ROSS MITCHELL

Newfoundland

Dr. O. H. Warwick, Director, National Cancer Institute, visited Newfoundland recently, and was guest speaker at Rotary. Whilst here he kindly consented to address the St. John's Clinical Society on the subject of Leukæmia and recent methods of treatment. It was a most informative and stimulating address, and greatly appreciated by the members of the St. John's Clinical Society.

Dr. C. A. Roberts, Superintendent, General Hospital, St. John's, was guest speaker at a recent dinner of the Kinsmen's Club. Dr. Roberts took as his theme—"Guard Your Health", and his address was very favourably received.

On February 21 the new Nurses' Residence at the Hospital for Mental and Nervous Diseases, St. John's was opened officially. This is an exceptionally fine modern building, and will add considerably to the facilities of this rapidly expanding hospital.

Dr. L. A. Miller, Deputy Minister of Health, has announced that four new motor vessels will be ready for medical service this summer. These ships will be stationed at points scattered along the South West Coast. Their chief function will be to pick up patients and bring them to hospital for medical attention. It is also hoped that regular inspection trips will be made with a doctor on board, at least once a month. Dr. Murphy of Belleoram will accompany one of the ships on the first trip.

Dr. J. Murray, who until recently, practiced in Harbour Breton, has taken up an appointment with the Colonial Medical Service in Uganda.

On March 1, a group of medical men opened the Medical Arts Building at Corner Brook. There are six two-room suites in the building, and x-ray, laboratory, and minor operating room facilities are available. There are five general practitioners with special interest in surgery, obstetrics, medicine and pædiatrics, anæsthesia and orthopædic surgery. An eye, ear, nose and throat man makes up the sixth member. The group hopes that this move will help improve the diagnosis and therapeutic facilities in this rapidly growing area.

J. C. SQUIRE

Ontario

Dr. James H. Baillie of Toronto has been appointed assistant medical director of the Bell Telephone Company. He will be in charge of health services in the Toronto area. He replaced Dr. Arthur B. Wright who has been associated with the company for twenty-one years, since 1944 as medical examiner and prior to that, as accident doctor. Dr. Baillie will also assist in the development and co-ordination of health services among Bell employees, in the company's western area.

The Department of Veterans' Affairs turned over the operation of Lyndhurst Lodge, Toronto, $100,000 treatment centre, to the Canadian Paraplegic Association on April 1. There will be no change in the treatment rendered; the same medical personnel will continue to direct operations. When treatment requirements include urological, orthopædic, plastic or neurological surgery the facilities of Sunnybrook and the general hospitals of Toronto will be used. Dr. A. T. Jousse is the medical director. One hundred and fifty paraplegic veterans have been treated there.

The population of Ontario Mental Hospitals as of January 1, 1950 was 18,408 patients. There is a waiting list of 2,121 applicants. Of these applications for admission, 1,969 are for the Ontario Hospital School at Orillia. There is one doctor for 209 patients; one psychologist for 1,225 patients, one occupational therapist for 243 patients, one social worker for 1,072 patients and one trained nurse for 37 patients. In addition there are 11 consulting physicians, 28 consultant specialists and 2 consultant psychologists.

Dr. T. G. Stoddart of Ottawa Civic Hospital has been awarded a Canadian-British exchange fellowship for study of cancer, tenable in England.

Dr. E. W. McHenry, professor of public health and nutrition, University of Toronto, reporting on recent health surveys among Toronto school children said that 40% of children in Toronto are not getting sufficient milk, while from 80 to 90% are getting very little vitamin D. This vitamin D is not available in any common foods; there is very little even in the flesh of fish. It must be obtained from halibut, cod or other fish liver oils.

The Royal Society of Canada has awarded the Sir Joseph Flavelle Medal for medical research to Dr. C. H. Best for his many important contributions to medical science. Queen's University at the Spring Convocation awarded the honorary degree of Doctor of Laws to Dr. Best.

Dr. Fredrick W. Jackson, director of health insurance studies in the federal health department, was awarded the 1950 gold medal by the Professional Institute of the Civil Service of Canada for outstanding contributions to national or world well-being.

Legislation which would give nurses more control over their own profession with regard to educational standards, curriculum and registration is again being sought by the Registered Nurses Association of Ontario. This is one of the matters to come up at the Silver Jubilee convention, held at the Royal York, April 27 to 29. The Ontario Government has failed to pass bills in the past few years in which the Association has asked that membership in the R.N.A.O. be compulsory for all nurses who register, and that the Association itself con-

duct registration, instead of having this done under the department of health. It is the old story of anybody being reluctant to yield authority. At some point the government took the power which in all the other Canadian provinces rests with the Nurses Associations and it is loath to part with the authority or the registration fees.

Dr. Shirley Fleming of Toronto has returned from a year in England spent in the study of anæsthesia. She is the first Canadian to obtain a Diploma of Anæsthesia since the examinations have been set in two parts. In a talk at the staff meeting of the Women's College Hospital she said that in most places general anæsthesia was preferred to local or spinal. Spinals were usually covered by a general and might be given after the patient had pentothal. In Edinburgh where spinals were in greatest favour they said there were fewer post-operative headaches when the patients had pentothal first. Hughston's visit in the summer had caused a stir of interest in epidural anæsthesia but in most places it had quickly waned. Several series of caudal anæsthesia in obstetrical cases were done but the method requires more full-time staff than most departments can provide. At Oxford it was used successfully for some patients with eclamptic toxæmia. Plastic tubing was used, technically this was a fussy procedure but the patients did well because the blood pressure fell.

The normal obstetrical patient gave herself gas and air with her pains. Many machines are designed for this, the principle is that the woman holds a finger over a hole in the intake and the mask on her face, as she loses consciousness this falls off. Trilene so far is given only under the direction of a physician, it gives only a light plane of anæsthesia and would be adequate for analgesia only.

In the teaching hospitals, except Edinburgh, some method of using ether was always evident. Cyclopropane was popular in some places and almost banned in others. A new synthetic called flaxedil is becoming popular. Its advantage was the shortness of the period of respiratory depression as compared with curare. Some anæsthetists, as Gray in Liverpool, thought that curare should always be followed by prostigmine regardless of the length of time which had elapsed since it had been given, the dose varied from 2.5 to 10 mgm. Patients who had it seemed to suffer from fewer gas pains.

A new development was the use of hylase, the enzyme of hyaluronidase for use in giving fluids directly into the tissues. The fluid is rapidly absorbed; the method is useful in pædiatrics and in patients with collapsed veins. An interesting investigation going on is the recording of electrocardiograms during intubation under various anæsthetics. The vagal reflex is being studied.

Any person in Ontario exposed to the hazard of silica in industrial operations other than mining, can be required to take a medical examination at any time. Cost of the examination will be borne by the employer. This bill was passed at the recent session of the legislature.

Mr. William Temple, CCF member of the Ontario legislature introduced a bill to require persons about to be married to undergo a test for syphilis. This was defeated 75 to 18.

The Humber Memorial Hospital, Weston, with 53 beds, costing $550,000 will be ready for use in November. A campaign to raise $80,000 is under way at present.

Ontario Municipalities have to pay about a dollar a day more for indigent hospital patients. Because of prepaid hospital plans less than 40% of public ward beds are occupied by indigents. The province pays $2.35 a day for every public ward bed in Toronto whether it is occupied or not.

Dr. C. M. Fletcher, Medical Research Council, Great Britain who was on his way home from a trip to Australia, addressed the Physiological Society, University of Toronto, on "Pneumokoniosis in Coal Mines" and later he spoke to the Ontario Diabetes Association. A Cambridge Blue, he discovered his own diabetes at the age of 30 and a shock it was to him. For many years he had been assuring patients to be of good heart as diabetes was quite amenable to treatment when his routine remarks suddenly became applicable to himself. His personal attitude to the situation is sensible, tough-minded and witty. The Association considered his speech worth saving and passing on to others so made a phonograph record of it which is available for a small fee.

Two hundred and seventy-two general practitioners registered for the postgraduate course in Medicine put on by the Ontario Medical Association at Sunnybrook April 3, 4, 5 and 6. Forty-eight papers were given. The papers were up-to-date and to the point with a practical outlook. Acoustics and ventilation were good and parking space was ample. LILLIAN A. CHASE

Dr. E. G. Turnbull, of Barrie was the recipient for 1949 of the Brydon Award. This award is given annually to the doctor in District No. 5, of the Ontario Medical Association, who has contributed most to the community and to medical societies. Dr. Turnbull has resided in Barrie since 1912 and has been in practice over forty years.

Ontario's tuberculosis detection services will be expanded with the purchase of four more mobile x-ray units. These will be based on the sanatoria in London, Weston, St. Catharines, and Fort William. The London unit will operate in 21 local centres. The Weston unit will work in neighbouring counties and in Muskoka and Parry Sound districts. The St. Catharines unit will work in the local factories and in the Lincoln, Welland and Haldiman Counties. The clinic based at Fort William will cover an area of more than 300,000 square miles and work especially in lumber camps. Electrocardiographic units are being purchased for the sanatoria in Cornwall, Fort William, Haileybury, Hamilton, Kingston, London, Ottawa and St. Catharines.

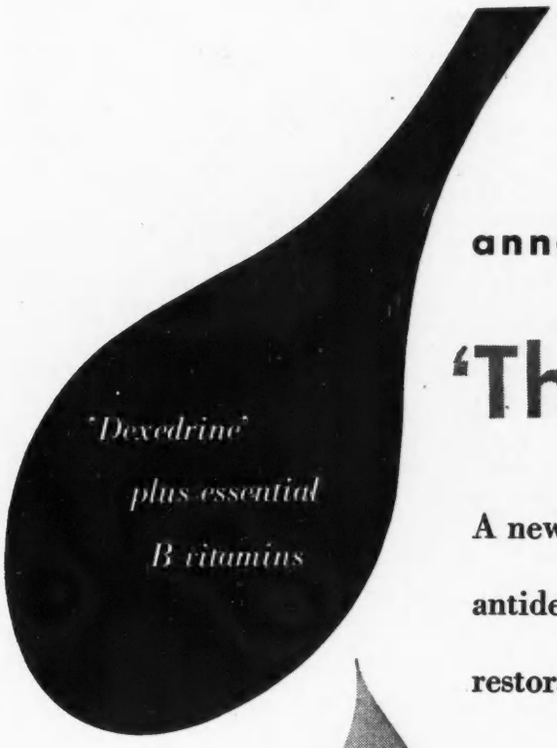
X-ray chest examinations for workers exposed to silica dust will be extended by the purchase of a mobile x-ray unit to provide follow-up examinations for men who are found to have chest conditions requiring observation or review more frequently than the regular examinations permit.

Three Ontario hospitals have been granted $533,112 to assist them in expanding their accommodations: These grants will enable the hospitals to increase their capacity by 381 beds and 20 infant bassinets. St. John's Convalescent Hospital, Newtonbrook, received $340,000, representing a grant of $2,000 for each of 170 new beds. The grant per bed is greater for hospitals which treat chronic cases than for the public general hospitals. Queen Victoria Hospital, North Bay, which is adding 93 beds and 20 infant bassinets to its facilities, will be granted $99,666, and St. Mary's on the Lake Hospital, Kingston, received $93,446, representing 50% of the cost of 118 beds. NOBLE SHARPE

Quebec

Le docteur Louis Lamoureux a été nommé chef du département d'anesthésie de l'hôpital Notre-Dame. Le docteur Lamoureux remplissait les mêmes fonctions au Queen-Mary Veterans' Hospital.

Le docteur Gilles Bertrand, boursier de la province de Québec, actuellment à Paris où il poursuit des études en neurologie et en neuro-chirurgie assistera au congrès des anatomistes de langue française qui se tiendra à Louvain au mois d'avril et y présentera un travail sur la circulation veineuse du cerveau. Le docteur Bertrand est également inscrit pour une communication au congrès d'Oxford en juillet prochain.



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L'American College of Surgeons a tenu récemment à Montréal son assemblée régionale. Plusieurs personnalités du monde médical y ont pris part. Les docteurs A. Ochsner de Nouvelle-Orléans, Marshall de Boston, Mason et Reynolds de Chicago, Selye, Browne, Miller, Philpott de Montréal étaient présents.

Le docteur Armand Frappier, directeur de l'Institut de Microbiologie et d'Hygiène de l'Université de Montréal, prononçait récemment une conférence devant l'Académie de Médecine de Toronto. La conférence du docteur Frappier porta sur la tuberculose.

Cinq médecins canadiens out reçu des bourses de la société canadienne pour la lutte contre l'arthrite et le rhumatisme. Ce sont les docteurs Joseph Blais de Montréal, Charles Brown de London, Rolland Côté de Roberval, J.-B. Fenwick de Winnipeg et le docteur DeGuise Vaillancourt également de Montréal. Les candidats poursuivront leurs études dans les plus importants centres européens et américains.

YVES PRÉVOST

New Brunswick

Dr. T. E. Grant of the Surgical staff of the Saint John, General Hospital will spend the next month in postgraduate study at the Mayo Clinic. The first fortnight of his stay will be devoted to gastro-intestinal cancer study on a grant from the N.B. Division of the Canadian Cancer Society, followed by two weeks' plastic surgery study.

Dr. W. A. Farrell radiologist of the Fredericton Hospital has been elected a member of the American College of Radiology.

Dr. Fred. L. Whitehead has assumed his duties as secretary of the N.B. Medical Society. Dr. Whitehead is a native of P.E.I., and graduated in medicine from Dalhousie University Medical School. He served in the R.A.F. and after demobilization practised in Parrsboro, N.S. For the last three years he has been secretary to the B.C. Medical Association.

The medical societies of St. Stephen, Saint John, and Moncton were privileged to hear Dr. Robert R. Linton, the distinguished surgeon of Boston, Mass., at their March Monthly Meetings. Dr. Linton spoke on the "Treatment of Peripheral Vascular Disease". Large audiences in each centre enjoyed Dr. Linton's visit and instruction in a subject of great interest.

Dr. F. H. George of Saint John was chosen to represent the R.C.A.M.C. on the officer escort for the Lieutenant Governor of N.B. at the opening of the Legislature at Fredericton. Major George commands the 34th Field Dressing Station Reserve.

Dr. R. F. Ingram of Bathurst is at present in New York on a refresher course in gynæcological cancer, on a Canadian Cancer Society grant from the N.B. Division.

Among N.B. surgeons attending the regional meeting of the American College of Surgeons at Montreal were: Dr. V. D. Davidson, Dr. T. E. Grant, Dr. John Finley, Dr. J. A. McLaughlin, Dr. W. A. Leggett of St. John; Dr. H. S. Everett and Dr. E. B. Johnston of St. Stephen; Dr. W. S. Fitzpatrick and Dr. H. E. Britton of Moncton; Dr. J. J. MacPherson and Dr. J. H. M. Rice of Campbellton; Dr. D. A. Thompson of Bathurst; and Dr. G. E. Chalmers of Fredericton.

A. S. KIRKLAND

Saskatchewan

Under the auspices of the Crippled Children's Program a clinic for treatment of cerebral palsy was officially opened on Wednesday, March 29. The Clinic is located in the Regina General Hospital and is an expansion of the work done in this field by the Canadian Red Cross. A Council for Crippled Children has been formed in Saskatchewan and it is hoped through the sale of Easter seals to establish a fund through which further cerebral palsy clinics can be established in the Province as well as facilitating treatment for children who are affected with other crippling disorders.

The Minister of Public Health, The Honourable T. J. Bentley, announced in the Saskatchewan Legislature that there was to be a charge of $10.00 for patients who attended the cancer clinics and who after investigation were found not to be suffering from cancer. The Cancer Control Act of Saskatchewan has been amended to give benefit to those people who actually suffer from cancer and no longer includes those who are thought to have cancer. This change has been found necessary in order to conserve the resources of the clinic for the cancerous patient. The cancer program in the Province of Saskatchewan is slowly being amended to broaden its effectiveness and to direct its efforts on sound lines.

Dr. and Mrs. J. G. Warren, Canora, were honoured by the residents of the district at a public gathering in Rainbow Hall at Canora. More than 300 persons attended the gathering and presented Dr. Warren with a silver tray with the inscription "Presented to Dr. J. G. Warren in appreciation of long, conscientious service as physician and surgeon, 1911-1950, Town of Canora". Residents of the Canora district and surrounding towns also presented Dr. Warren with a silver ink stand. Dr. and Mrs. Warren plan to make their new home in Hamilton, Ontario.

Dr. Donald C. McEwen of Regina has been awarded a two year fellowship to study cancer. The fellowship was established in honour of the late Dr. Allan W. Blair, a leader in development of cancer clinics and treatment centres in Saskatchewan. Dr. McEwen is now studying at Churchill Hospital in Oxford, England, and plans to continue study of abdominal surgery and gynæcological cancer in Britain, Scandinavia, the United States and Canada.

Dunnet Lake will soon appear as a place name on Saskatchewan maps in tribute to Dr. Henry Watters Dunnet who served the people of Avonlea for 38 years. The newly-named lake is in the Forbes Lake area, 50 miles north of Lac la Ronge.

G. G. FERGUSON

General

The Third Annual Meeting of the American Association of Blood Banks is being planned for October 12, 13, 14, at The Stevens Hotel in Chicago. The central location was chosen so that the meeting will be more accessible to members from all points of the country. The program which is being planned will be one which will attract blood bank personnel, hospital executives, pathologists, clinicians, surgeons, and other people interested in the procurement, preservation, and administration of blood and blood derivatives. For further information write the Office of the Secretary, 3301 Junius Street, Dallas 1, Texas.

The American Physicians' Art Association will have its twelfth art exhibition in conjunction with the American Medical Association Convention at San Francisco Auditorium, June 26 to 30, 1950. Any physician who follows the hobby of fine or applied arts can exhibit at this convention by becoming a member of the A.P.A.A. and applying for entry blanks and shipping labels of the secretary F. H. Redewill, M.D., 526 Flood Bldg., San Francisco, 2, Calif.

Third Annual Symposium on Orthopædic Appliances. Plans are well under way to convene in Pittsburg the Third Annual Symposium on Orthopædic Appliances.

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The meetings have been set for the week of September 18, 1950. This Symposium will once more be a co-operative undertaking of the Department of Orthopædic Surgery of the University of Pittsburgh's School of Medicine and Mellon Institute's Multiple Fellowship on Orthopædic Appliances sponsored by the Sarah Mellon Scaife Foundation. Inquiries concerning final program details and requirements for attendance should be addressed to the Orthopædic Appliances Fellowship, Mellon Institute, 4400 Fifth Avenue, Pittsburgh 13, Pa.

The First International Congress of Clinical Pathology is being held in London, July 16 to 20, 1951. Provisional sectional programs (bacteriology, pathology, hæmatology and chemical pathology) are being prepared and look very interesting. Apart from the other aims of such a Congress, it is desired to show that hospital pathology, as practised in Great Britain, has a very high standing and gives ample opportunity for original investigation. A warm welcome will be extended to Dominion representatives.

The activities of the Plastic Surgery Section of the IX Asamblea Nacional de Cirujanos will he held from November 19 to 25, 1950, at the Hospital Juarez in Mexico City. The meeting of the American Society of Plastic and Reconstructive Surgery will be held in Mexico City November 27, 28 and 29, 1950, immediately after the work of the Plastic Surgery Section of the IX Asamblea Nacional de Cirujanos. The management of this meeting will be in charge of the American Directors. Each group may execute their work according to their usual procedures. To this date approximately 400 plastic surgeons have been invited to attend and a group of them have been specially requested to present papers in our section.

The Tenth International Congress of Dermatology will be held in London during the summer of 1952, under the Presidency of Sir Archibald Gray. A preliminary program will be prepared during the current year. As a result of the disruption produced by the last war, addresses of the Secretaries of certain Dermatological Societies are not available, so that all those interested are asked to communicate with Dr. G. B. Mitchell-Heggs, general secretary, at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W.C.2.

The American Congress of Physical Medicine will hold its twenty-eighth annual meeting and clinical session August 28, 29, 30, 31 and September 1, 1950, inclusive, at the Hotel Statler, Boston, Massachusetts. All sessions will be open to members of the medical profession in good standing with the American Medical Association. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

Book Reviews

Proceedings of the First Clinical ACTH Conference. J. R. Mote. 607 pp., illust. $5.50. The Blakiston Co., Philadelphia and Toronto; Doubleday Publishers, Toronto.

This volume is a testimonial to the amazingly rapid strides which can be made when a research program gets under way in a large number of centres. In 1946 the Armour Laboratories first made their limited supplies of pure adrenocorticotrophic hormone (ACTH) available to clinical research teams in the United States and Canada. As supplies became slightly more plentiful, the tempo of investigation accelerated and the hormone was supplied more freely to groups of investigators with the basic stipulation being that facilities for controlled observation must be available. By the fall of 1949 it became evident that all the groups working in the field would benefit by direct mutual discussion of the results so far obtained. Accordingly, Dr. John R. Mote of the Armour Laboratories called a conference in October. This book presents, in almost verbatim form, the proceedings of that session. Its publication within five months of the actual meeting is no mean achievment. As one reads the various papers presented it becomes apparent that the value of ACTH to Medicine lies not only in its dramatic effects on many diseases, but also in the manner in which it forces us to reconsider many of our basic concepts of disease processes. The *Proceedings* is not intended as a guide to practical therapeutics. Indeed, it would do much harm if so interpreted. This is a collection of research papers, of interest to all who are concerned with medical progress and, of course, invaluable to those laboratory and clinical workers in any way interested in this field.

Its early publication is a tribute to the editor, Dr. Mote; its contents are an example of scientific co-operation at its best.

Neuroradiology. A. Orley, Honorary Consulting Radiologist, West End Hospital for Nervous Diseases, London. 421 pp., illust. $14.25. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1949.

Neuroradiology has developed rapidly, and is still doing so. New techniques are being devised, and old ones changed. The techniques and methods described in this book are different to the ones generally used in America in many respects, and it is difficult to evaluate them. The methods used to demonstrate various parts of the skull are outlined and excellently illustrated. The various types of lesions seen on plain films are described and illustrated. There is an excellent section on cerebral angiography. The method of pneumoencephalography is simple, but slow. It consists of taking multiple films of the ventricles as the air is being injected. Multiple projections from many angles are then used to show the various parts of the ventricles rather than stereoscopic films in standard positions. No doubt both methods have their advantage. There is an excellently selected bibliography and index.

Cystoscopy and Urography. J. B. Macalpine, lately Honorary Surgeon and Surgeon in Charge of the Genito-urinary Department, Salford Royal Hospital. 554 pp., illust., 3rd ed. $15.75. John Wright & Sons Ltd., Bristol; Macmillan Co. of Canada Limited, Toronto, 1949.

This is a splendid text, the greater part of which is devoted to cystoscopy. It should prove valuable to the experienced urologist, especially if in a teaching position because of the excellent exposition of fundamental principles which it contains. The novitiate will find it equally useful both because of the careful description of cystoscopic technique and of the common pitfalls which beset the beginner as well as the lengthy descriptions of the various lesions which may be found within the bladder. Throughout the book the author's broad experience and knowledge are apparent. There are interesting and informative descriptions of the etiology and pathology of the commoner disease processes affecting the urinary tract so that the book does not fall short of becoming a text of Urology itself. In an excellent chapter on bladder tumours the author recommends the large cystoscopic rongeurs for biopsy purposes and the fulgerating electrode for treatment. He fails to draw attention to the resectoscope which is now widely employed both for the purpose of biopsy and the removal of even very large lesions.

In the section on prostatic enlargement attention is directed to the desirability of not instrumenting these patients preoperatively by catheter or cystoscope, so that the operation can be performed in a sterile field. The lack of preoperative instrumental interference forms the basis of so-called "aseptic prostatectomy".

Continued on page 54

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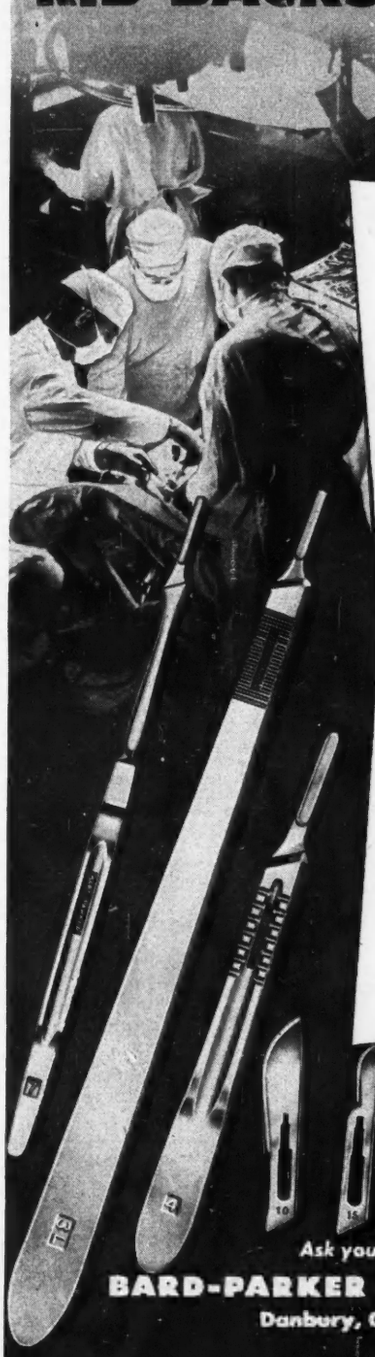

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OBJECTS: To assist in the defence of its members in cases of alleged malpractice, and to encourage honourable practice in the daily work of the medical profession.

Subject to our by-laws, assistance is given by the payment of the taxable costs of actions together with reasonable counsel and witness fees in cases undertaken by our Association, as well as damages if awarded. All members in good standing of the Canadian and various Provincial Medical Associations may be enrolled upon signing the application form and paying the annual fee. All other regularly qualified practitioners must have their application countersigned by two members of our Association.

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in the year....., and a duly licensed practitioner

of the Province of..... I am also

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Signature .....

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Recommended by two members of the Association, unless applicant is a member in good standing of the Canadian or any Provincial Medical Association.

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Books Received

Continued from page 528

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

First Aid Manual No. 1. Sir H. E. Whittingham and Sir S. Cade. 300 pp., illust., 9th ed. 75c. Macmillan & Co. Ltd., London and Toronto, 1949.

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